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Proceedings of the Royal Society of Medicine

OCCASIONAL LECTURE

Demonstration-Lecture on X-ray Cinematography [1]

By RUSSELL J. REYNOLDS, C.B.E., M.R.C.P., D.M.R.E.

ABSTRACT.—The author describes a practical method of X-ray cinematography by which permanent records may be rapidly and inexpensively obtained.

A photograph is taken of the screen-image by an ordinary cinematographic camera and by the use of continuous bands of positive film movements may be studied for any length of time. The advantage of this is specially obvious when examining such organs as the heart. These permanent records can be used for the following purposes :—

1. Diagnostic.
2. To compare with former records, in order to watch effects of treatment, or progress of a pathological condition.
3. For teaching purposes.
4. For transmission at home or abroad, so that they can be examined by other specialists who may wish to see what the former condition was.

The process is simple enough to become routine practice in hospitals and institutions, and to be within the reach of every radiologist.

The apparatus occupies only a small space, can be accommodated in any X-ray department, and can be operated by one person.

The method is perfectly safe as far as the patient is concerned; that is to say there should be no difficulty in avoiding excessive exposure to radiation.

RÉSUMÉ.—L'auteur décrit une méthode pratique de cinématographie radiologique au moyen de laquelle il est possible d'obtenir des images permanentes rapidement et sans grands frais.

On fait une photographie de l'image sur l'écran au moyen d'un appareil cinématographique ordinaire, et en employant des bandes continués de film positif on peut étudier les mouvements pendant longtemps. L'avantage de ceci est surtout évident quand il s'agit d'étudier des organes tels que le cœur. Ces régistres permanents peuvent être employés pour les buts suivants :—

1. Pour le diagnostic.
2. Pour comparer avec des régistres précédents, pour surveiller les résultats thérapeutiques ou le progrès d'une affection pathologique.
3. Pour l'enseignement.
4. Pour envoyer dans le pays même ou à l'étranger pour permettre à d'autres spécialistes, qui peuvent désirer connaitre l'état précédent du malade, de les examiner.

Le procédé est assez simple pour être adopté comme routine dans les hôpitaux et les instituts, et pour être à la portée de tous les radiologistes.

L'appareil occupe peu de place, peut être logé dans n'importe quel département radiologique, et peut être manœuvré par une seule personne.

La méthode est absolument sans danger pour le malade—c'est-à-dire qu'il ne devrait exister aucune difficulté à éviter une exposition trop prolongée aux rayons X.

ZUSAMMENFASSUNG.—Verf. beschreibt eine praktische Methode der Röntgenkinematographie die dauerhafte Dokumente schnell und billig herzustellen erlaubt.

Das Schirmbild wird mit einem gewöhnlichen cinematographischen Apparat photographiert, und mittels ununterbrochener Bänder von positiven Film kann man Bewegungen

[1] At a meeting of the Society, held May 1, 1934.

durch lange Zeit beobachten. Besonders klar ist der Vorteil dieser Methode bei der Beobachtung von Organen wie das Herz. Diese dauerhafte Dokumente können für die folgenden Zwecke dienen .—

1. Für die Diagnose.
2. Zum Vergleich mit früheren Aufnahmen um therapeutische Erfolge zu kontrollieren oder den Verlauf eines pathologischen Zustandes zu beobachten.
3. Für den Unterricht.
4. Für Sendung in das In- oder Ausland damit andere Spezialisten die den früheren Zustand wissen wollen sie betrachten können.

Die Methode ist so einfach dass sie als Routine in Kliniken und Instituten gebraucht werden kann, und ist jedem Radiologe zugänglich.

Das Apparat nimmt wenig Raum ein, kann in jeder Röntgen-abteilung Platz finden, und kann durch eine Person in Gang gesetzt werden.

Für den Patient ist die Methode ganz ungefährlich, das heisst, es müsste ganz leicht sein übermässige Aussetzungen und die Strahlenwirkung zu vermeiden.

I AM not going to weary you with a long account of the experiments in X-ray cinematography, carried out during the past thirteen years, but shall confine myself to giving you a description of my recent experiments and showing you the results.

We are indebted to the late Dr. John MacIntyre of Glasgow for the first idea of X-ray cinematographic effects ; he showed movements of the bones of small animals in 1897.

My first experiments in connexion with X-ray cinematography were made thirteen years ago—in May 1921. Impressed with the extreme value that a cinematographic effect should have in studying the movements of joints in health and disease and the functioning of various organs, especially the heart, I conducted some experiments with a view to bringing the principle of cinematography into practical use in connexion with the X-ray examination of the living body. If its application is to come into general use, the methods employed must be simple, expeditious, and relatively inexpensive.

Rapid serial skiagrams may be obtained by two distinct methods : (1) the direct method, and (2) the indirect method. In the direct method a rapid series of skiagrams is taken on a band of film by the action of X-rays after passing through the subject under examination, as in ordinary radiography. This method is, of course, very costly, on account of the size of the film required and the mass of apparatus which has to be employed in order to manipulate it. For this reason my attention was directed to the development of the indirect method. In this, an actual photograph is taken of the shadow cast by the object under examination on a suitable fluorescent screen. An ordinary cinematograph camera is used, fitted with the necessary adaptation required for this special purpose.

Details of the experiments conducted from 1921-1925 are set out in a thesis presented to the University of Cambridge in September of the latter year. Experiments conducted at a later date were described in a paper communicated to the *British Journal of Radiology* on December 22, 1926, and in a paper read at the twenty-eighth annual meeting of the American Roentgen Ray Society at Montreal, in September 1927, and published in the *American Journal of Roentgenology*, vol. 19, No. 5, May 1928.

To achieve success many difficulties had to be overcome, and three essential conditions had to be fulfilled :—

(1) Obtaining a sufficiently brilliant screen image to record on a cinematograph film.

(2) Cutting off the direct beam of X-rays passing through the screen, so that only ordinary light could reach the film.

(3) Ensuring that the subject under examination was not exposed to an excessive amount of radiation.

The problem of these three essential conditions has only recently been satisfactorily solved.

Partial success was achieved as early as September 1925, when I obtained records of movements of the thorax and various joints of the body with a relatively long exposure. Improvements in apparatus and technique have been made from time to time since that date, both by myself and by workers abroad. Mention may be made of the work of Janker, Naegeli, Wohlleben, Schade and others.

It was almost impossible to obtain any satisfactory results in the case of movements of the abdominal viscera and it is only recently—since the introduction of improvements in the manufacture of X-ray tubes, of lenses, of fluorescent screens and cinematograph films—that our difficulties have been considerably modified, and experiments have been conducted which have led to X-ray cinematography becoming

FIG. 1.—General lay-out of the apparatus.

a really *practical* achievement. I have now been able to obtain cinematographic records of the movements of the alimentary tract—particularly I would mention the stomach and duodenum. These improvements in apparatus have also incidentally been the means of improving the results in the case of parts of the body which I was able to show previously. Fortunately, it has been found that it is only necessary to protect the camera and films from radiation by a suitable thickness of lead. The lens itself proves to be sufficient protection against direct rays reaching the film by this route. The third essential condition, viz., the protection of the subject under examination from injury due to excessive exposure to radiation, has been rather more difficult to fulfil. However, by developing the means I employed as far back as 1925, I have ensured that radiation from the tube is only emitted during the period of time that the camera shutter is open. In this way the

patient does not receive more than 50% of the radiation to which he would be subjected if the X-ray tube was working continuously. In other words, I have "synchronized" the working of the X-ray tube with the movements of the camera shutter. It is now possible to expose patients to radiation for a sufficient length of time to obtain a suitable length of cinematograph film, to record full movements of the parts under examination, without in any way risking their safety.

A total exposure of sixteen seconds to one area has been given, and this has been repeated within a few days, without any ill-effects on the patient at all. I have fully described the early forms of the synchronizing apparatus in the publications mentioned above.

The present device for making and breaking the primary current is very simple.

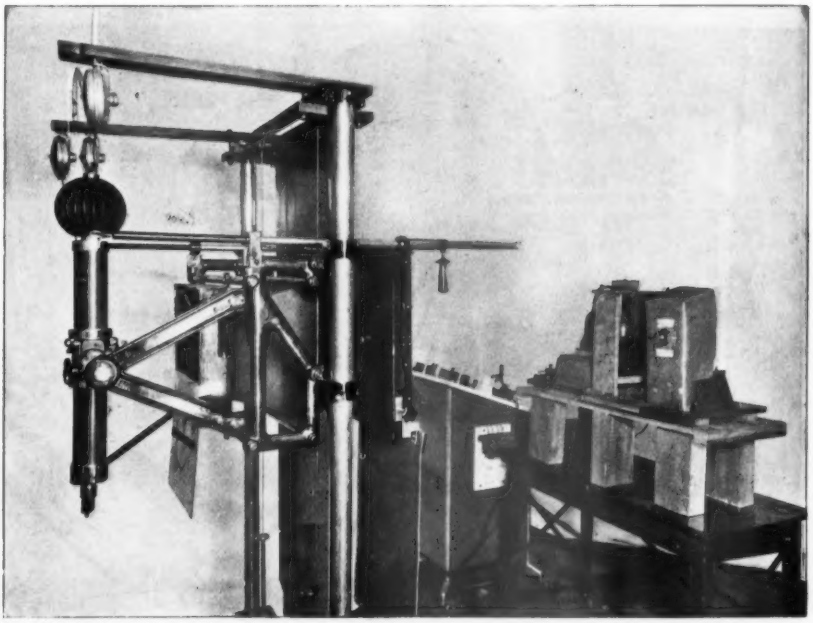

FIG. 2.—View showing X-ray tube in position and lead shield to protect the camera.

It consists of a series of contacts around a rotating disc made of insulating material. The axis of the disc is continuous with the spindle of the cinematograph camera and the whole is driven by an electric motor, the speed of which can be varied. This ensures perfect synchronization.

At present a 20-kilowatt metalix tube is used as the source of radiation. The power plant is a one-valve unit kindly supplied by Messrs. Watson and Sons. A Zeiss lens, with aperture of 0·85, fitted with a micrometer screw collar for adjusting the focus is attached to a 16 mm. standard cinematograph camera. I am indebted to Messrs. Dallmeyer for carrying out this part of the work. The special screen and specially coated film have been manufactured for me by Messrs. Ilford, who have kindly helped me in many ways with their advice and technical assistance.

A very large amount of experimental work had to be done before the present results were obtained.

To give an idea of the possibilities of this method, a first-class cinematograph film of a dried skull can now be obtained with 60 frames a second, that is to say, each exposure was 1/120th of a second.

A 16 mm. cinematograph camera has been used during the later experiments, thus securing a process simple enough to become a routine practice in hospitals and institutions, and well within the reach of every radiologist. The apparatus occupies only a limited space and can readily be accommodated in any X-ray department. It can easily be operated by one person. It is wholly unnecessary to have a long length of film; in actual practice, *a small length can be made up into a band and*

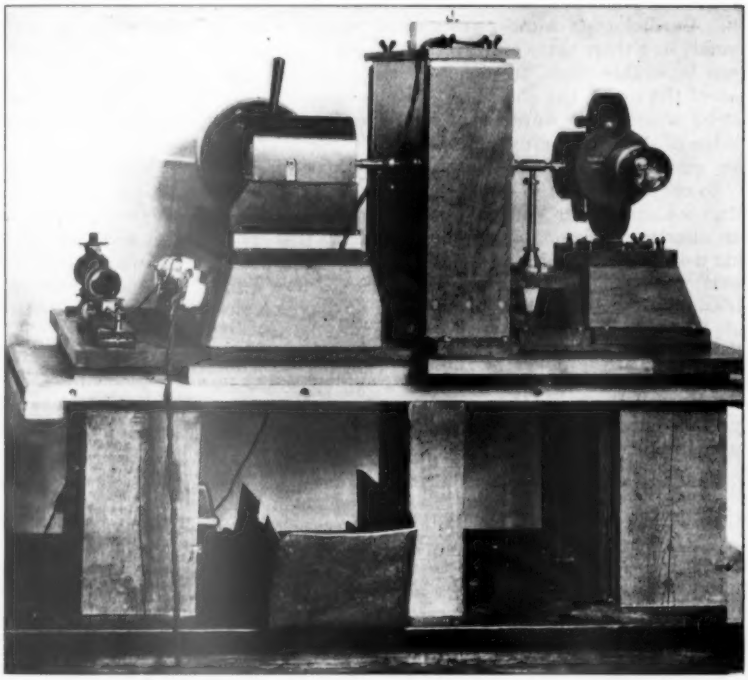

FIG 3.—The photographic unit with synchronizing switch.

run through the projector continuously, enabling cases to be studied at leisure. It is obviously only necessary to give a sufficiently long exposure to obtain a record of the movements desired; this can be done, in most cases in a very few seconds, on a piece of film a foot or more long. The resulting negative can be printed off again and again on a length of positive film.

The expense of production is small—much less than would be the case if a standard-sized film were employed. A non-inflammable acetate film is used, so that there is no necessity for any special protection against fire; its use does not come under the special regulations of the county councils. The image produced can be projected either natural size or enlarged as desired.

There would appear to be a large and varied field for research in this new method of X-ray diagnosis; it is at present impossible to estimate the potentialities.

It should prove, for example, of immense value in investigating lesions of the lung and pleuræ, especially after lipiodol injections, or in cases in which artificial pneumothorax has been induced. As regards movements in the alimentary tract in pathological states, the advantage of being able to study such movements indefinitely, after the administration of an opaque medium is obvious. In orthopædic lesions the range of movements in limbs and joints can be observed after an injury, and in those cases where an operation has been performed progress can be recorded and studied at intervals.

Ordinary X-ray examination has been regarded for many years as a recognized and even essential method of investigating the condition of the cardiovascular system. Cardiologists almost invariably include such an examination as a routine when analysing their cases; up to the present time, however, the chief use of X-rays has been to enable them to check-up their physical signs as regards the size and position of the heart, the condition of its cavities, and the state of the great vessels; it must be admitted, however, that X-rays have so far contributed very little to our knowledge of the functioning of the organ.

The cinematographic method of investigation, however, will, I believe, add greatly to our knowledge of the functioning of the heart, especially in the various irregularities arising in cardiac lesions, for instance, in sino-auricular block. I propose shortly to demonstrate the value of this method for cardio-analysis by showing a slow-motion film, correlated with graphic records of the heart's action.

Apart from the clinical uses mentioned, there are, of course, other fields of usefulness, for instance the investigation of physiological problems where use may be made of opaque media injected into the circulatory system in animals.

The apparatus that I have here is not the one I have used for the film I am going to show you, but so long as the output is sufficient any power unit will do.

[Dr. Russell Reynolds then gave a working demonstration of the apparatus, and during the development of the film-record thus taken, showed a series of cine-radiographic studies.]

Dr. ROBERT JANKER (Bonn) said that he had employed, and partly modified, both the direct and the indirect methods of X-ray cinematography. By the direct method, only small objects had been taken, the rate of exposure being 22 films per second. By the indirect method he had produced many films of laboratory animals showing physiological and pathological reactions. Some of these films were taken at the usual rate; with others the movement of the organs could be shown with faster or slower motion as needed for observation.

Great care had been taken to improve each factor in the making of the pictures. He (Dr. Janker) had constructed a highly efficient X-ray apparatus for the exposures, using a Schering-Kahlbaum screen, and cinematograph apparatus of his own construction, in which specially adapted lenses were used. At first he had sensitized the films himself, but later he used Kodak SS films, or films with a Schleussner X-ray emulsion.

[Photographs of the various apparatus were shown, and also cinematograph skiagrams of the heart, blood-vessels, lungs and process of digestion in various animals.]

Section of Comparative Medicine

[*February* 28, 1934]

Malaria from a Zoological Point of View

By Sir RICKARD CHRISTOPHERS, C.I.E., M.B., F.R.S.

ABSTRACT.—Protozoal parasites occurring in the red cells of mammals are: Hepatozoon, Babesia, Theileria and Plasmodium. The frequency with which these forms occur differs considerably in the different mammalian orders. But whilst there is a relationship apparent between the mammalian stem and the form of parasite, there appears to be an even closer association with the type of blood-sucking arthropods which the mode of life of the animals in a particular stem favours. Ungulates in the days of their greatest development chiefly roamed in herds over rather arid country not favouring mosquitoes, but suitable for tick infestation. Monkeys and bats are more likely to live in a humid sheltered environment where they are more liable to attack by mosquitoes.

Knowledge of the plasmodial parasites of monkeys has up to recently been very meagre, but from the work of Sinton and Mulligan it appears certain that in the main distinct parasites occur respectively in the Oriental and Ethiopian regions, just as the genera of monkeys under present nomenclature are mainly confined to one or other of these zoogeographical realms. *P. brasilianum* occurring in the Neotropical monkeys is a distinct parasite from any Old World form. None of the monkey parasites are probably really very close to those of man.

The apes evolved as part of a great Pliocene fauna, and their remains occur in Europe, Egypt and India. The progenitors even of the present-day African forms are found in the Indian deposits. In the gorilla and chimpanzee, forms of plasmodium, so far described, appear to be very similar to those of man, including the characteristic crescent forms.

In the main the races of men are essentially Pleistocene and Palæarctic. They none of them form true Neotropical, Australasian or Oriental man in the zoological sense, but it is less certain there is not a relationship in the case of the Ethiopian region. The parasites of malaria in any case do not show any apparent relationship to the usual zoogeographical realms, and their distribution and prevalence appear to be determined on quite other grounds than those normal to zoological distributions. *P. vivax* occurs almost throughout the world within the July and January isotherms of 60°. *P. falciparum* is limited by the isotherms of 70°. Quartan is believed by Knowles and Senior White to have a peculiar geographical distribution. Frequency of occurrence is, however, entirely different from distribution, and this parasite probably also has its distribution determined by factors other than those usually concerned in the distribution of animal forms of life. Among other features it appears to be associated with areas of severe endemicity, and becomes conspicuous when transmission is temporarily in abeyance. Mer has recently shown that it has a very slow development in the mosquito, and this may explain some of its peculiarities.

The parasites *P. tenue* and *P. ovale* are so far recorded only from India and East Africa respectively. Observations regarding the occurrence of these forms are much needed.

RÉSUMÉ.—Les parasites protozoaires qui se trouvent dans les globules rouges des mammifères sont : Hepatozoon, Babesia, Theileria et Plasmodium. La fréquence des différents parasites varie beaucoup selon les ordres des mammifères. Quoiqu'il existe une relation apparente entre la souche mammifère et le type de parasite, une relation encore plus étroite semble exister entre le type d'arthropode suceur de sang et la mode de vie des animaux d'une certaine espèce. Les ongulés, pendant la période de leur plus grand développement, erraient en troupeaux à travers les plaines arides peu favorables aux moustiques, mais favorisant l'infestation par les tiques. Les singes et les chauves-souris demeurent probablement dans des lieux humides et abrités, où ils sont plus exposés à l'attaque des moustiques.

Nos connaissances sur les plasmodes des singes ont été très maigres jusqu'à present, mais d'après les travaux de Sinton et Mulligan il semble certain qu'en général des parasites différents sont trouvés dans les régions orientale et éthiopienne, de même que les genres de singes, d'après la nomenclature actuelle, sont en général limités à l'une ou l'autre de ces régions zoogéographiques. *P. brasilianum*, trouvé dans les singes néotropiques, se distingue de tous les types de parasite de l'ancien monde. Il est probable qu'aucun des parasites du singe se rapproche beaucoup de ceux de l'homme.

Les singes se sont développés comme une partie de la grande faune Pliocène, et leurs restes ont été trouvés en Europe, en Egypte et aux Indes. Même les ancêtres des types africains actuels se trouvent dans les excavations aux Indes. Les types de plasmode trouvés jusqu'ici chez les gorilles et les chimpanzés semblent se rapprocher beaucoup de ceux trouvés chez l'homme, y compris les formes caractéristiques en croissant.

En général les races humaines proviennent essentiellement des époques pléistocène et paléo-arctique. Aucune d'elles ne représente le vrai homme néotropical ou australasien ou oriental dans le sens zoologique, mais l'absence de relation est moins certaine dans le cas de la région éthiopienne. En tout cas les parasites du paludisme ne montrent pas de relations avec les régions zoogéographiques, et leur distribution et leur fréquence semble être déterminée par des principes entièrement différents de ceux qui agissent normalement dans la distribution zoologique. *P. vivax* existe à peu près partout entre les isothermes de 60° F. en janvier et juillet. *P. falciparum* est limité par les isothermes de 70° F. Knowles et Senior White croient que le parasite de la fièvre quarte a une distribution géographique particulière. Toutefois la fréquence et la distribution sont des choses entièrement différentes, et la distribution de ce parasite est probablement aussi déterminée par des facteurs différents de ceux qui agissent dans la distribution des animaux. L'une de ses caractéristiques est qu'il paraît être associé avec des régions de haute endémicité, et se fait remarquer quand la transmission est temporairement en suspens. Mer a démontré récemment qu'il se développe très lentement dans le moustique, ce qui explique peut-être quelques-unes de ses particularités.

Jusqu'à présent *P. tenue* a été trouvé seulement aux Indes et *P. ovale* en Afrique orientale. Des observations sur la distribution de ces deux types sont très nècessaires.

ZUSAMMENFASSUNG : Die protozoische Parasiten die in den roten Blutkörperchen der Saugetieren vorkommen sind : Hepatozoon, Babesia, Theileria und Plasmodium. Die Häufigkeit dieser Formen ist in den verschiedenen Saugetieren sehr verschieden. Während eine scheinbare Beziehung zwischen dem Stamm der Saugetieren und der Form der Parasiten besteht, scheint diese eine viel nähere Beziehung zu besitzen mit den blutsaugenden Arthropoden die durch die lebensweise der Tiere eines bestimmten Stammes bevorzugt sind. Die Ungulaten wanderten zur Zeit ihrer grössten Verbreitung über eher trockene Ebenen, die den Schnaken nicht, dagegen aber den Schecken günstig waren. Affen und Fledermäuse wohnen gewöhnlich in einer feuchten, geschützten Umgebung, wo sie dem Angriff von Schnaken mehr ausgesetzt sind.

Unsere Kenntnis der Plasmodien der Affen ist bis jetzt sehr gering, aber nach Sinton und Mulligans Arbeiten scheint es sicher zu sein dass verschiedene Parasiten in der orienental bzw. äthiopische Regionen, ebenso wie die Affen, nach der heutigen. Nomenklatur, meistens auf eine oder die andere von diesen zoogeographischen Gebieten beschränkt sind. Das in den

neotropischen Affen vorkommende *P. brasilianum* unterscheidet sich von allen Parasiten die in der alten Welt vorkommen. Wahrscheinlich sine keine von den Affenparasiten den menschlichen Parasiten sehr nahe verwandt.

Die Affen haben sich als Teil der grossen Pliozänfauna entwickelt, und man findet ihre Resten in Europa, Ägypten und Indien. Die Vorfahren selbst der heutigen afrikanischen Affen sind in den indischen Niederschlägen zu finden. Die bisher in den Gorillen und Schimpanseen beschriebenen Plasmodiumformen scheinen den menschlichen Formen sehr ähnlich zu sein, einschliessend der charakteristischen Halbmondformen.

Im ganzen sind die menschlichen Rassen wesentlich Pleistozan und Palaarktisch. Es gibt keine echte neotropische, australasische oder orientale Menschen im zoologischen Sinne, aber in dem Äthiopischen Gebiet ist es weniger sicher dass keine Beziehung besteht. Jedenfalls zeigen die Malariaparasiten keine deutliche Beziehung zu den gewöhnlichen zoogeographischen Gebieten, und ihre Verbreitung und Häufigkeit scheinen auf ganz andere Faktoren begründet zu sein als die normalen zoologischen Verbreitungen. *P. vivax* wird fast in der ganzen Welt zwischen den Januar- und Juli-Isothermen von 60° F. gefunden. *P. falciparum* ist durch die Isothermen von 70° F. eingeschränkt. Knowles und Senior White glauben dass das Quartanfieber eigenartig verbreitet ist. Häufigkeit und Verbreitung sind jedoch ganz verschieden, und die Verbreitung dieses Parasites ist wahrscheinlich auch durch andere Faktoren bestimmt als andere Lebensformen. Unter anderen Charaktere scheint er mit Regionen grosser Endemizität verbunden zu sein, und er wird auffällig wenn die Übertragung vorübergehend nicht aktiv ist. Mer hat in letzter Zeit gezeigt dass dieser Parasit sich in den Schnaken sehr langsam entwickelt, was einige seiner Eigentümlichkeiten vielleicht erklärt.

P. tenue ist bisher nur in Indien, *P. ovale* nur in Ostafrika gefunden. Beobachtungen über diese zwei Parasiten sind sehr notwendig.

MAN, along with many of the lower animals, is subject to the invasion of his red blood corpuscles by certain parasitic protozoa. Infection with *Plasmodium* in man constitutes the important disease, malaria. Infection with *Piroplasmidæ* in cattle gives rise to some of the most important diseases dealt with by veterinary science. Other parasites of this kind are found in various domestic and wild animals, among which we may specially mention the parasites giving rise to monkey malaria.

Except for a few peculiar forms, about the nature of which little is known, protozoan parasites of the red cells are all at present considered to fall in the Class Sporozoa, Subclass Coccidiomorpha. In other words, as suggested by Wenyon, 1926 [1] for the Hæmosporidiidæ, they are coccidia which have taken to parasitism of the red cells of the blood instead of the more usual epithelial host cell favoured by these parasites. Judging by the accepted classification of the Sporozoa, this habit is one that has developed more than once in the course of evolution. In every case this habit is associated with, and has probably necessitated, the passing of a part of the life-cycle of the parasite in an intermediate invertebrate host.

The three chief groups of red-cell parasitic sporozoa are, the Hæmogregarinidæ, the Hæmosporidiidæ and the Piroplasmidæ. In general, the Hæmogregarinidæ are commonest in the lower vertebrates, such as reptiles and fish, and have only been known relatively recently in mammals since Balfour, 1905 [2], described a typical form in the jerboa. Of the two families of the Hæmosporidiidæ, the Hæmoproteidæ are very common in birds, but are known also in reptiles and the Plasmodidæ are perhaps more especially mammalian forms, though they are also common parasites of birds and a few forms seemingly of this type are known in lizards. The Piroplasmidæ are entirely mammalian.

The genera occurring in mammals are: (in the Hæmogregarinidæ) *Hepatozoon*, including all the hæmogregarine-like forms attacking either the red cells or the leucocytes; (in the Piroplasmidæ), *Babesia* and *Theileria*; (in the Hæmosporidiidæ), *Plasmodium*.

In the accompanying table, compiled from the list of mammalian hosts given by Wenyon, 1926 [3], are given under the different mammalian orders, the number of species in which parasites of each of these kinds have been recorded. The exact

	Hepatozoon	*Babesia*	*Theileria*	*Plasmodium*
Monotreme			1	
Marsupial	4			
Insectivora	1	3		2
Chiroptera		3		14
Primatia	2	2		26
Rodentia	29	14		5
Carnivora	6	11		2
Ungulata	2	30	3	2
Edentata		1		

numbers should not be given too much weight, but the table gives a good general idea of the distribution of these parasitic forms in the different mammalian stems. In marsupials, so far only *Hepatozoon* has been described, though a *Theileria* is recorded in the Monotreme *Echidna*. Possibly, however, the number of marsupials examined has not been very great. Among the placentate mammals *Hepatozoon* occurs most noticeably in the Rodents and also in the Carnivora. *Babesia* (with *Theileria*) is almost the only form occurring in Ungulates, though at least two Plasmodia and two Hepatozoa appear to be authentically recorded in this order. Carnivora and also Rodents rather frequently show *Babesia*-like parasites, as also the Insectivora and Chiroptera. The Bats and especially the Primates are very noticeable for the frequency with which they show *Plasmodium*.

The very early mammals were of aplacentate or marsupial type. The placentate orders are known from the Eocene (Zittel, 1925 [4]). The most primitive of the early prototypes were the Primitive Insectivors from which are derived the existing Insectivors, the Bats, Primates and Rodents. The Carnivora arose from the Creodontia, a primitive carnivorous type, now extinct, having affinities with the Primitive Insectivors. The Ungulates are derived from another primitive stem, the Condylarthra, which had affinities with the Creodonts and in some cases with the Rodentia. In general, stems much as at present existed throughout the tertiary, some, however, becoming extinct.

It is possible perhaps to regard these derivations as giving some explanation of the relative prevalence of type of parasite. Thus one might explain the occurrence of *Babesia* in both Ungulates and Carnivora as due to both these stems arising from creodont ancestors, whilst *Plasmodium* in Bats and Primates might be ascribed to the common insectivor ancestry of these orders. It cannot be said that such explanations are very convincing. A more likely line of approach is suggested if we consider the intermediate invertebrate hosts with which stems are likely to be more especially associated.

The Ungulates and Carnivora are notably tick carriers. The vast droves of game, which we may visualize as occurring when the ungulates with their attendant carnivors were undergoing evolution, would lead to a life in the main remote from water, probably in steppe- or park-like country. Under such conditions the maximum facilities are likely to be given for the evolution of parasites based on the tick as intermediate host. Birds, bats and monkeys tend to live among trees, in wooded and even forest country and would be more brought into contact with mosquitoes. Allowing that plasmodial parasites once specialized to a particular mammalian stem would tend to be restricted to this stem, the idea that evolution of parasitic forms was from the intermediate host seems to be most in keeping with the known facts. It also receives support from the consideration sometimes pointed out that it is usually the sexual stage which is passed in the invertebrate host. From this point of view, then, we may regard man as continuing to harbour parasites of his red cells

which were acquired at some remote period when his ancestors or precursors, ape, monkey, lemur or primitive insectivor, lived in close association with anopheles, probably in the forest. It remains to be seen whether we can glean anything from what is known of plasmodial forms in the primate stem as to the probable source from which the parasites of man came. The data we possess suggests that it was much more likely to be from some part of the primate stem than any casual picking up of a parasite from outside this stem.

Monkey malaria.—The lemurs are the most primitive of the primates. Their remains are known from the Eocene in Europe and America, but they disappear from the fossil record until they are found again in Pleistocene and recent times in Madagascar. A few recent forms such as *Tarsius*, occur also elsewhere. So far as I have been able to ascertain, no plasmodial or other red-cell parasites have been described from lemurs. Anaplasma-like bodies are described by Dodd, 1913 [5], but are not considered by this author to be of parasitic nature.

The remaining primates are divided into the Catarrhini (Old World apes and monkeys) and the Platyrrhini or New World monkeys and marmosets. These are two distinct stems, the latter isolated at an early period and now forming part of the Neotropical or South American fauna. Fossil monkeys are known from the Oligocene in Egypt (*Parapithecus, Moeripithecus*). *Oreopithecus* is known from several localities in Europe in the Upper Miocene. A number of fossil catarrhine forms occur in the Pliocene in Europe, Asia and Africa.

The existing Old World monkeys include a number of genera, the nomenclature of which has become so confused that it is sometimes difficult to trace what genus is intended by an author. Recently, a revision of the parasite-bearing forms has been made by Stiles and Nolan, 1929 [6], whose nomenclature most authors dealing with monkey malaria now follow. Since a good deal of interest is at present being taken in monkeys on account of monkey malaria, yellow fever, etc., I give a list of generic names according to Stiles and Nolan, with the English names of the monkeys and their rough distribution.

CATARRHINI (Old World Apes and Monkeys).

Anthropomorpha (Higher Apes).

Pan	Chimpanzee	Africa
Gorilla	Gorilla (2 species)	,,
Pongo	Orang-Utan	Borneo, Sumatra
Hylobates	Gibbons (4 to 5 species)	India, Sumatra, Borneo, etc.
Symphalangus	Siamang	Sumatra

Cynomorpha.

Colobus	Guereza Monkeys	Africa
Pygathrix	Langurs	India, Sumatra, Java
Papio	Baboons	Africa
Theropithecus		Abyssinia
Macaca	Barbary Ape	North Africa
Silenus (Macacus)	Macaques	India, Sumatra, China, etc.
Cercocebus	Mangabeys	Africa
Cercopithecus	Guenon Monkeys	,,
Erythrocebus	,, ,,	,,

PLATYRRHINI.

Cebidæ (Spider Monkeys).

Aotus	Titi Monkeys	S. America
Callicebus	Saki Monkeys	,,
Pithecia	Uakari Monkeys	,,
Cacajao	Squirrel Monkeys	,,
Saimiri		,,
Cebus	Capuchin Monkeys	S. and C. America
Lagothrix	Woolly Spider Monkeys	S. America
Brachyteles	,, ,, ,,	,,
Ateles	Spider Monkeys	S. and C. America
Alouatta	Howler Monkeys	,, ,,

CATARRHINI (Old World Apes and Monkeys) *continued.*

Callithricidæ.

Leontocebus	Tamarins	S. America
Mystax	,,	,,
Ceneocebus	,,	,,
Œdipomidas	Marmosets	C. America
Mico	,,	S. America
Callithrix	,,	,,

The generic name used by these authors for the Langurs is *Pygathrix* (not *Semnopithecus*); *Macaca* refers only to the Barbary ape; *Silenus* is the valid generic name for the macaques. The common macaque is therefore *Silenus rhesus* and the oriental monkey often called *Cynomolgus irus*, from which a number of parasites have been described, is *S. irus*. *Pygathrix* and *Silenus* are oriental forms and *Papio*, *Cercocebus* and *Cercopithecus* African forms.

Knowledge regarding the plasmodial parasites of monkeys was also until recently in a very confused state, so that little could have been said regarding type of parasite in the different genera or their distribution. The revision of Oriental and African plasmodia of monkeys recently published by Sinton and Mulligan, 1933 [7] has, however, made the nature of the different parasites encountered in monkeys much clearer and one can also form tentative conceptions regarding their distribution. Excluding parasites of the great apes which will be referred to later, the following are valid named species and varieties of plasmodial parasites described from monkeys as given by the above authors.

Plasmodium kochi	Cercocebus (?)	Africa
var. bouilliezi	Cercopithecus	,,
var. joyeuxi	,,	,,
var. macfiei	Papio, Cercopithecus	,,
Plasmodium inui	Silenus	Oriental
var. cynomolgi	,,	,,
var. gonderi	Cercocebus	Africa
Plasmodium knowlesi	Silenus	Oriental
Plasmodium semnopitheci	Pygathrix	,,
Plasmodium brazilianum	Cacajao (Brachyurus)	S. America

Forms resembling *P. vivax* and *P. malariæ* are also described in *Ateles* respectively in Central America, by Clark, 1930 [8].

In the main the Oriental and African forms are distinct. Var. *gonderi* is, however, African, though it is classed as a variety of *P. inui*.

It will be well at this point both for the better understanding of the distribution of monkey malaria and later for the appreciation of points connected with the malaria parasites of man and the higher apes to outline briefly some features in the distribution of animals which have a bearing on the question we are now dealing with viz. from whence did man obtain his malaria parasites.

As is well known, animal life on the globe is distributed mainly in accordance with certain great faunal realms or regions, often with very well-defined boundaries within which all forms of life have a certain facies, species, genera, or even higher divisions, being peculiar to them. These realms are: the Australasian, the Neotropical, the Ethiopian, the Oriental, the Palæarctic and Holarctic, and a so-called Transitional, or Mediterranean, realm, which though generally treated as a subregion of the Palæarctic, may in certain groups, e.g. in Anopheles, appear as a rather important and distinct primary subdivision.

That these realms are to a large extent palimpsests of past geological phases appears certain. Thus the Australasian region appears to have been isolated before the placentate mammals reached the region. The strange South American

or Neo-tropical region is the result of isolation from the Eocene to the Pleistocene.

In regard to the areas we are most interested in to-night it may be said that in the Upper Miocene a fauna, characterized by such forms as the tapir, stretched from Spain in Europe far to the east, where in the Malayan region at the present day its features are traceable. Following upon this in the Lower Pliocene a great development of mammalian forms took place in Eastern Europe and Western Asia, forming a fauna whose features at the present time are evident in the existing African fauna. This fauna is represented in the great fossil beds of the Siwaliks in India and extended into China and the East where it has left a mark in some of the features of the recent fauna. In the Pleistocene a slow recession of the Pliocene fauna took place with the advancement of Palæarctic forms leading to the existing arrangement. That the replacement was very slow is shown by many facts, as for example that the hippopotamus was still present in the Pleistocene in Germany, and that the lion and the hyena were driven out of Europe by man.

As we have seen the Old World monkeys first occur in the Miocene of Europe to which continent they are supposed to have come from Africa (Zittel, loc. cit.) They later form a prominent element in the Pliocene fauna, fossil forms much resembling those of the present day being found in Europe, India, etc.

Though there is a general resemblance between the parasites of monkey malaria and human malaria, as there is, it may be well to remember, between those of bird malaria and human malaria, yet the characteristic *P. falciparum* type has not yet been recorded from any monkey. Probably the parasites of monkeys are not really very close to those of man.[1]

Malaria parasites of apes.—The apes first appear in the Oligocene and fossil remains apparently ancestral to the gorilla and chimpanzee occur in the Pliocene in Europe and India. At the present-day apes are represented in the East by the gibbons and the ourang-utan and in Africa by the chimpanzee and two species of gorilla.

A number of observations have been made on malaria parasites in these animals. Halberstaedter and Prowazek, 1907 [10], record a parasite named by them *P. pitheci* from the ourang-utan in Borneo. Other writers have confirmed this for other areas. From the description and figures available there seems at least a possibility that crescentic forms occur. Reichenow, 1920 [11], in the Cameroons describes *P. vivax* and *P. falciparum* in the gorilla and all three forms of human malaria parasites in chimpanzees. Blacklock and Adler, 1922 [12], in Sierra Leone found in a chimpanzee a parasite indistinguishable morphologically from *P. falciparum* and also transient infection with *P. vivax*- and *P. malaria*-like forms. As, however, they failed to infect two Europeans with the blood from the chimpanzee they considered the parasite to be distinct from the human form and named it *P. reichenowi*. Adler, 1923 [13] examined thirteen chimpanzees caught in Sierra Leone and found two infected with parasites indistinguishable from *P. falciparum*, in both cases crescents being present. That these parasites are not due merely to chimpanzees contracting human malaria appears evident from the difficulty with which the animals can be infected, if at all, with human malaria experimentally.

1 All attempts to infect the lower monkeys with human malaria have failed. The only successful transmission to any lower animal is the transient infection with *P. vivax* in the chimpanzee described by Roubaud (loc. cit.). Injection of blood containing monkey parasites (? *P. knowlesi*) into three human volunteers by Knowles and Das Gupta gave rise to a mild, medium and severe infection respectively. Clark 1931 [9] failed with blood and infected mosquitoes to infect human volunteers with monkey infections found by him. Owing to some resemblance between *P. knowlesi* and *P. ovale* I injected at Col. S. P. James's suggestion a monkey (*S. rhesus*) on two occasions with human blood containing *P. ovale*. Though on the second occasion parasites were in very large numbers no infection resulted. The monkey, however, later readily contracted infection with *P. knowlesi* when this parasite was injected.

Mesnil and Roubaud, 1920 [14], attempted to infect chimpanzees by intravenous inoculation with *P. vivax* and *P. falciparum*. They obtained a transient infection in one case with *P. vivax* but in no case any result with *P. falciparum*. They also failed to infect by the bite of infected mosquitoes with *P. falciparum* sporozoites in the glands. Blacklock and Adler, 1924 [15], injected 3 c.c. of human blood with numerous *P. falciparum* into a young chimpanzee but without result.

In the natural infection of apes we find for the first time a close similarity to the parasites of human malaria with the presence of crescentic gametocytes. It is in the ape stem, which is distinct from the other monkeys as far back as the Oligocene (*Propliopithecus*), that one finds for the first time really suggestive evidence of the origin of man's red-cell parasites. It is interesting to note that not only are *P. falciparum*-like parasites present, but that in the chimpanzee three forms very like those of man occur.

The malaria parasites of man.—Early forms of man (*Pithecanthropus, Eoanthropus, Sinanthropus*), appear first in the Pleistocene or at the earliest in late Pliocene. Such forms have been found in very widely separated localities, Java, England, China, etc. Modern man (*Homo sapiens*), though distributed throughout the whole earth, appears to be of Palæarctic origin. True Australasian, Neotropical or Oriental man, in the sense we have been using these terms, almost certainly does not exist. Whether the negro race may be regarded as in any way representing Ethiopian man in this sense is perhaps more uncertain.

To an even greater extent than man himself the distribution of his malaria parasites gives little or no indication of any ordinary zoogeographical relationship. The three common parasites, *P. vivax*, *P. malariæ* and *P. falciparum* appear now to have an almost world-wide distribution, limited only by the existence of temperatures suitable to their transmission by the intermediate host. According to Knowles and Senior White, 1930 [16], the limits of distribution of *P. vivax* are determined by the July isotherm in the northern hemisphere of 60° F. and that of *P. falciparum* by the July isotherm of 70° F. In the southern hemisphere a somewhat similar relation holds good to the January isotherm.

Quartan according to Knowles and Senior White has a peculiar distribution. Though limited as a dominant parasite by the same isotherm as *P. falciparum* its distribution is spotty and shows a tendency to follow a zone of high humidity. It occurs according to them especially in forest regions, islands in the tropics and seashores of subtropical climates and is especially associated with aboriginal inhabitants of countries and areas of high endemicity. They regard this as an older parasite than the other two parasites of man and one that is dying out, *P. falciparum* being the most recently acquired and *P. vivax* holding an intermediate position.

Even with quartan, however, it would seem that the distribution is determined by considerations quite other than those ordinarily determining the distribution of forms of animal life. Though its frequency may be greater in some conditions than others its occurrence is almost if not quite as widespread as the other two parasites. As claimed by Knowles and Senior White it is usually most conspicuous in areas of high endemicity, and hence perhaps as a result in aboriginal tribes and intense foci generally. It is in my experience usually especially conspicuous where owing to temporary drought, etc., other parasites in an intense focus have become reduced in number. Hence it appears to be a parasite with a greater tenacity of hold than the other parasites, at least in untreated communities. Recently Mer, 1934 [17], has found the cycle of development of quartan in the mosquito to be extraordinarily slow, a feature which, combined with its resistance to natural eradication from its host, may account for some of the peculiarities in its distribution.

Whilst, however, the known distribution of these three common malaria parasites of man has not yielded so much information as we might have expected, there is little doubt that the final word has not been said and the possibility of much more emerging when we have learnt better how to distinguish differences in parasites must not be overlooked.

In 1914 Professor J. W. W. Stephens [18] described a peculiar parasite from India which from its very amœboid form he named *P. tenue*. Sinton, 1922 [19] later gave further information about this parasite and showed that the peculiar amœboid form was not its only or its most important point of distinction. Working among aboriginal tribes in the jungly Singhboum tract I considered in a report made by me at that time (Christophers, 1925 [20]) that the parasite I was dealing with was largely, if not almost entirely, *P. tenue*. The more complete establishment of the validity of this species and, if its validity and means of identification is established, its distribution, have still to be worked out.

In 1922 Professor Stephens [21] described another new malaria parasite of man from East Africa which he named *P. ovale*. The validity of this has been shown recently beyond all doubt by the researches of James, Nicol and Shute, 1932 [22], and we can now await with some confidence the working out of its distribution. Is this species confined to Africa? If so it would be a point of very great interest.

This paper is perhaps already overcharged with hypothesis and I rather hesitate to introduce anything further of this nature. The absence of crescent forms in monkeys and their presence in the great apes and man is, however, a very striking fact, the implications of which are very far reaching. In the first case, of course it gives support to the view that the great apes and man constitute a rather independent evolutionary stem, as indeed its geological record shows. Further, it is very suggestive of Africa as the possible original home of malaria. Even if dissemination of the malaria parasites throughout the world was not merely the result of spread from Africa through the movements of modern man, it is still a possible hypothesis that malaria arose in Palæarctic man when he impinged on the fringe of the Pliocene African fauna and acquired the parasites of older types of man ancestrally associated with the great apes.

A theory may be useful even if not true if it stimulates the acquisition of facts. What has been said does suggest the value of certain information at least. We want to know more about the parasites of the orang-utan and the gibbons. Also whether there exist peculiar parasites in indigenous races of such isolated regions as New Guinea. Again, historically, more might perhaps be ascertained as to how malaria reached America. It is a long way and very far north for spread from Asia. When was malaria first known in the United States and under what circumstances? Was it known before the importation of negroes from Africa? Was it known in South America when this continent was first reached from the west? It might be possible to ascertain by historical research some facts of this nature and any results obtained would have a considerable interest.

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Section for the Study of Disease in Children

President—F. C. PYBUS, M.S.

[*February* 23, 1934, *continued.*]

Amyoplasia Congenita.—ALAN MONCRIEFF, M.D., and PHILIP WILES, F.R.C.S.

Male infant, born 26.10.33 in Queen Charlotte's Hospital.

Family history.—One other child in family, normal. Parents not related; said to be normal except for some vague illness of the mother as a girl, when one leg was under treatment for two years. During pregnancy with this child mother's health excellent. Urine normal throughout. Presentation was a vertex; right occipito-posterior which rotated easily. Labour lasted nine hours. Membranes ruptured spontaneously, and were normal. No evidence of any excess or deficiency of liquor amnii.

Patient's history.—Child weighed 7 lb. 10 oz. at birth and measured 21 in. in length. The deformity of feet and hands was noted at birth and the shoulder defect observed a few days later. Skiagrams taken at the age of three weeks showed no bony abnormality. Provisional diagnosis made of multiple contractures at joints, referred to Mr. Wiles at the Queen's Hospital for Children. Diagnosis of amyoplasia congenita made.

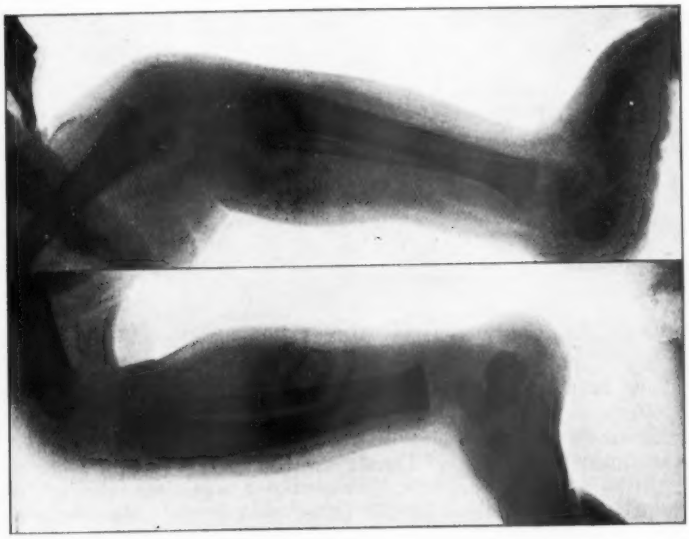
Present state.—Aged four months. Has developed normally in weight and in mentality since birth. Heart and lungs normal. Kidneys not felt; urine normal. Left side of abdomen appears to bulge a little. Head normal in size, shape and consistency.

Deformities.—Contractures are present, affecting nearly every joint of the limbs.

1.—Upper limb: both scapulæ elevated giving rise to appearance of very short neck; movements of shoulders greatly restricted. Right elbow has full range of movement. Left elbow: extension beyond a right angle impossible. Wrists apparently normal. Fingers are all flexed and cannot be straightened. Additional deformity of metacarpo-phalangeal joint of thumb (see X-ray pictures).

2.—Lower limb: full extension of the hips is limited by about 45°. ? dislocation of left hip present. Knees: full extension of right knee limited by about 45°. Left knee cannot be extended beyond a right angle. Both feet are in severe valgus position.

X-ray examination (9.2.34).—No abnormality in structure of bones. Relative position of both scapulæ and of thumb bones abnormal. High position of left great trochanter. Upper part of chest is somewhat compressed and heart shadow appears larger than normal. Comparison with X-ray appearances of the limbs of a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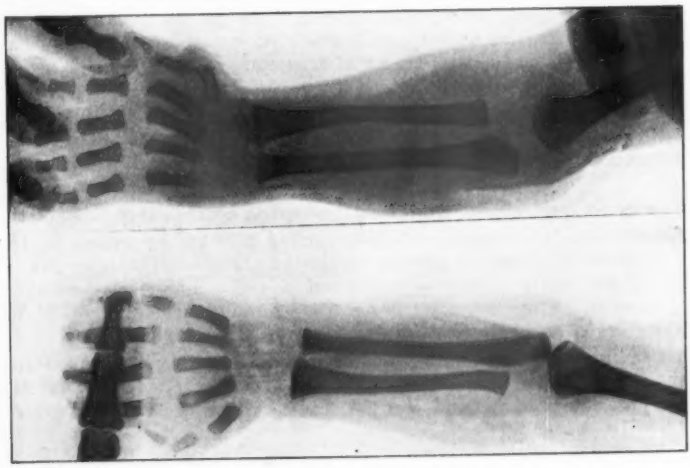
Patient.
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normal child of the same age suggests definite defective and irregular development of the muscles in the present case.

Electrical reactions.—All the muscles reacted normally to faradism except the left gluteus, both sets of peroneus muscles, both deltoids, extensor communis digitorum (right) and extensor longus pollicis (right). The erector spinæ also reacted weakly. No reaction to faradism could be obtained from the extensor communis digitorum (left) and extensor longus pollicis (left). Those muscles, reacting weakly, or not at all, to faradism, responded to galvanism. No reaction of degeneration is present.

Comment.—This condition is characterized by "multiple congenital articular rigidity" (Sheldon [1]) and is variously known as amyoplasia congenita, myodystrophia fœtalis, arthrogryphosis multiplex congenita and multiple articular rigidity. There may be a very wide distribution, as in this case, or only one or more groups of joints, usually symmetrically, may be involved. The joints may be found either in flexion or extension, according as to which muscle group is predominating. Very typical, however, is the ulna adduction of the fingers and the anterior dislocation of the metacarpo-phalangeal joints of the thumbs.

The disease was originally considered to be a primary disease of joints. More recently it has appeared as a myopathy, although the actual abnormality of muscle seems to be quantitative rather than qualitative. Stewart Middleton [2] has drawn attention to the resemblance to a sporadic disease occurring in sheep. Should the two prove to be identical, it will be of great interest, because Fraser Roberts [3] has been able to show by selective breeding that in sheep the condition depends upon "the homozygous state of an autosomal recessive factor." D. S. Price [4] describes a case of a child, which came to autopsy, in which there was extensive degeneration of the spinal cord with signs of chronic inflammation. Although this casts doubt upon the disease being primarily one of muscle, it is difficult to accept a neuropathic origin without further confirmation.

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A Form of Gigantism with Splanchnomegaly.—Wilfrid Sheldon, M.D.

The patient is a boy, aged 3 years and 5 months.

Family history.—He is the last of a family of five. There have been no miscarriages. The first three children weighed 10 lb. at birth, the fourth weighed 9½ lb., and the patient at birth weighed 11 lb. The first child died when 5 days old, the other surviving children are said to be healthy.

Past history.—When the patient was 15 months old he was noticed not to be able to support himself, and he was X-rayed at the Edinburgh Hospital for Sick Children, where he was reported to have "a lump in the middle of his spine." He was then put on a spinal frame, on which he lay until 3 years of age, when he was brought to London. By that time there was no evidence of spinal disease.

He cut his first tooth at 7 months, and was able to say a few words at 1 year, but has made no progress with talking since then. There has been no history of vomiting, or of anything to suggest headaches. His eyes are said to have been "always very hazy."

Present condition.—Skeleton. The boy is big for his age, his total length being 37½ in. The head is large and of unusual shape. The maximum circumference is 21 in. (normal 19 in.), and the measurement over the vertex from one external auditory meatus to the other is 14½ in. (normal 12 in.) There is some bossing of the frontal bones, and considerable bossing above the ears (as in osteogenesis imperfecta), while the face and jaws are remarkably broad. The eyes are wide apart, the bridge of the nose is broad, and the teeth are widely spaced apart (figs. 1

FIG. 1.—Photograph of patient, showing the coarse features, and the outline of the large liver and spleen.

and 2). The pituitary fossa is unusually large but not deepened, and the clinoid processes do not appear to be eroded.

The arms give the impression of being short and thick. The measurement from the acromion process to the styloid process of the radius is 10½ in. X-ray examination shows the long bones of the arms to be broad and massive, and the head of the humerus is set at more nearly a right angle to the shaft than normal. (See fig. 3.) Skiagram of the leg bones appears normal. From the anterior superior spine of the ilium to the internal malleolus measures 14½ in.

The hands and feet are broad, and skiagrams show the metacarpals to be broader than normal. The spine shows a diffuse lordosis throughout the dorsal and lumbar regions, but this may be due partly to the fact that the boy has not yet learned to sit up.

Teeth.—The teeth, in addition to being spaced far apart, are hypoplastic, and the incisors are cone-shaped.

Eyes.—Both corneæ are opaque, owing to epithelial dystrophy, the epithelium staining diffusely with fluorescin. The diameter of the corneæ is 14 mm. instead of the normal 11·6 mm., and the anterior chamber is deep. The pupils react to light and accommodation, but it is impossible to see the fundi. (Mr. L. H. Savin.)

FIG. 2.—Skiagram of skull showing the long flat pituitary fossa.

Hair.—The scalp hair is thick, coarse and dry—quite unlike the normal hair at that age. The eyebrows are also thick and prominent.

Liver and spleen.—The spleen is considerably enlarged, extending three finger-breadths below the costal margin. The organ is firm, with a smooth surface. The liver is also enlarged, extending below the costal margin to the same level as the spleen. In addition, the right lobe has a tongue stretching downwards and forwards nearly to the crest of the ilium (? Reidel's lobe). The surface of the liver is smooth. The kidneys cannot be felt.

Testicles.—The right testicle is in the scrotum, but the left testicle cannot be felt.

Other systems.—The heart, lungs, urine and nerve reflexes appear normal. For several months there has been persistent nasal discharge, and recently bilateral otorrhœa. The tonsils and adenoids are small, and the maxillary antra are clean.

Mentality.—The boy is bright enough to play with toys, and makes crooning noises to himself, but he cannot sit up or talk. He can see, and if he wants anything he will gesticulate energetically until he gets it.

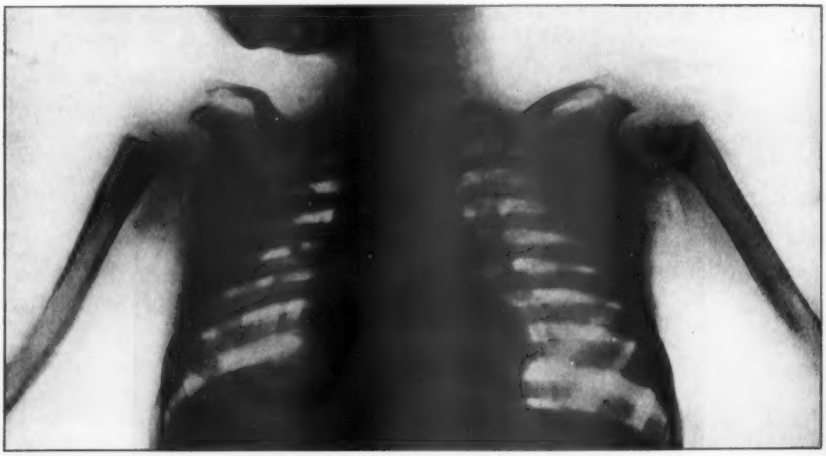


FIG. 3.—Skiagram to show abnormal shape of upper end of humeri.

Investigations.—Wassermann reaction of both patient and mother negative.

Blood-count: R.B.C. 6,100,000; Hb. 94%; W.B.C. 9,400; Polys. 36%; lymphos. 62%. Blood calcium: 10 mgm. per 100 c.c. Blood phosphorus: 4 mgm. per 100 c.c.

CREATININE AND CREATINE OUTPUT IN TWENTY-FOUR HOURS SPECIMEN OF URINE

	Volume of urine	Creatinine	Creatine
Patient	... 125 c.c.	50 mgm.	36 mgm.
Control child of same age	... 364 c.c.	140 mgm.	110 mgm.

The volume creatinine/creatine ratios are practically the same in both children.

Discussion.—Dr. REGINALD LIGHTWOOD said that he had demonstrated a case in which the clinical appearances exactly matched those in Dr. Sheldon's case; i.e. the skeletal abnormalities, the splanchnomegaly and the facial aspect. A hoarse voice and corneal haziness appeared to be additional characteristics of this condition which would, doubtless, soon have to be recognized as a separate entity.

Dr. R. W. B. ELLIS said that in addition to the case mentioned by Dr. Lightwood he had seen two others that resembled Dr. Sheldon's case extremely closely. One of these was that of a Lithuanian girl, aged 7, and one that of a boy, reported elsewhere.[1] The common features

[1] *Proceedings*, 1934, xxvii (Clin. Sect.)

in this group appeared to be the cranial and facial conformation, mental deficiency, and enlargement of the liver and spleen. The pituitary fossa was not grossly abnormal in the two cases referred to, and apart from the appearance of the head, the general physical development would not justify the description of gigantism.

ADDENDUM.—Since I reported this case, Dr. Cockayne has kindly drawn my attention to an article by Helmholz and Harrington, in which similar cases of this syndrome are recorded. (Helmholz, H. F., and Harrington, E. R., *Amer. Journ. Dis. Child.*, 1931, xli, 793.)

Congenital Malformation of the Neck. (Klippel-Feil's Disease or Web-Neck.)—ERIC PRITCHARD, M.D.

H. C., female, aged 3 months. This appears to be a typical case of Klippel-Feil disease. There is considerable congenital deformity of the cervical spine, with apparent spina bifida and deficiency of vertebræ. Owing to difficulty in getting

FIG. 1.—Showing webbed appearance of skin between left mastoid and acromial processes when put on the stretch by forcibly flexing the head to the right.

FIG. 2.—Showing spina bifida and other abnormalities of cervical vertebræ.

sufficient extension of the head, the defects in the vertebræ do not show very clearly in the skiagram. The head, with very little neck, appears to be sunk into the thorax, and there is definite webbing between the mastoid and the acromial processes. As is usual in these cases there are other concomitant congenital malformations—i.e. cleft-palate and pre-auricular nodule.

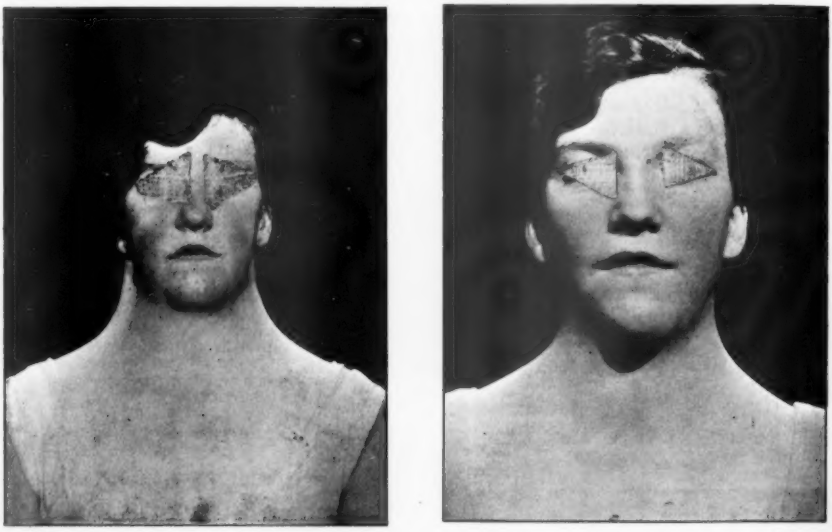


FIG. 3.—Sir Harold Gillies' Case.
(*a*) Before operation. (*b*) After operation.
All the scars of this operation are placed behind the web and as near the hair margin as possible.

Sir HAROLD GILLIES said that he had had three cases of this condition, who as young adults, had sought an improvement of appearance. Two had been operated upon, one not. The two operated upon had shown an immense improvement. He did not find any mental deficiency in any of the cases, merely a depression from psychic reasons. No X-ray examination had been made of any of the patients, as the defect had appeared to be in the skin and fascia of the neck. The relief of the condition had been obtained by a plastic operation on the skin and deep fascia. In each of the cases the prolongation of the hair extended down the neck along the posterior aspect of the web. He hoped that members would be interested in the cosmetic relief of this very ugly deformity which was well represented in the photograph taken before the plastic operation (fig. 3*a*).

Congenital Stenosis of the Hepatic Duct.—J. V. BRAITHWAITE, M.D.

History of patient.—L. N., male, aged 1 year. First admitted to Leicester Royal Infirmary 3.6.33, aged 5 months, suffering from jaundice which he had had for three weeks, which was becoming more intense. There was no vomiting and he was taking food well. The urine was deep red in colour, and the stools pale. On the day before admission purpuric patches were noticed on the legs by the child's mother.

Previous history.—Full-time child, normal delivery, weighed 8¾ lb. at birth. No jaundice during early infancy.

Family history.—Father, mother, and four children all well; no deaths; one miscarriage; no history of tuberculosis.

Condition of patient on admission.—Nutrition normal; jaundice marked; liver enlarged, reaching 1 inch below costal margin; spleen palpable. Large area of purpura behind left knee, and smaller one behind right knee.

Urine: contained bile, pus and *B. coli*.

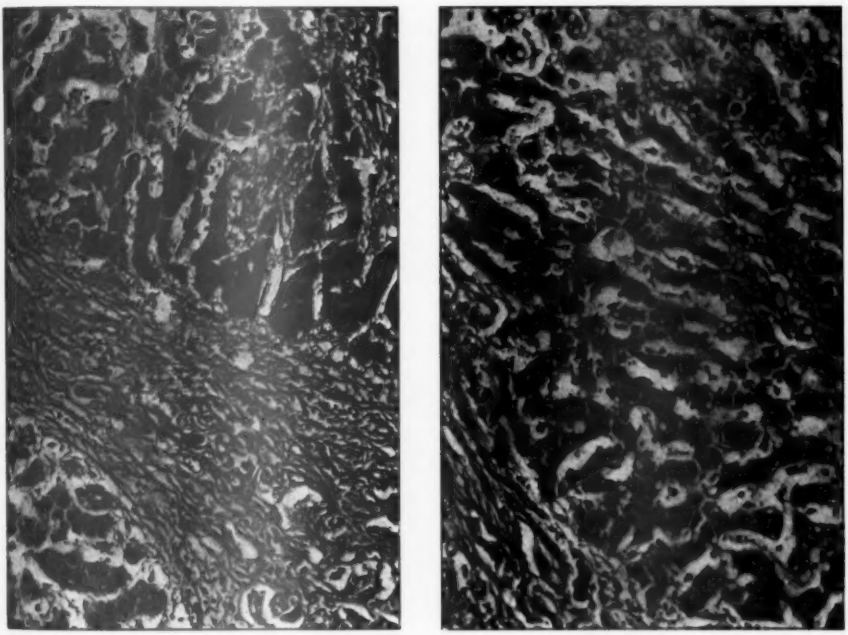
Blood: no increased fragility of red cells; Hb. 70%; red cells 4,432,000 per c.mm.

Progress of patient.—There was no pyrexia. The jaundice decreased and the child improved, and was discharged.

25.7.33.—Seen in out-patient department: no obvious jaundice, but stools pale.

1.1.34.—Readmitted, aged 12 months. Jaundice had returned since August and had become intense. The child was taking food well. The abdomen was distended and the liver enlarged. Van den Bergh reaction: immediate direct. Wassermann reaction ±. Blood: Hb. 69%; red cells 5,000,000 per c.mm.; white cells 9,600 per c.mm.; reticulocytes 2·3%; platelets 256,000 per c.mm. Urine: Bile present, *B. coli* and staphylococci present.

Pneumonia developed and the child died six days after admission.



Liver: Showing monolobular cirrhosis.

Post-mortem examination.—Brain: dura, cerebrospinal fluid, choroid plexus all stained yellow. Larynx: congested and swollen. Lungs: pneumonic consolidation of left upper lobe. Heart and great vessels: bile-stained.

Liver: Enlarged; stained deep green with bile, and shows a fine cirrhosis.

Gall-bladder collapsed and pale, containing "white-bile." The cystic duct is a little constricted at its junction with the common hepatic duct, where there is a plug of inspissated bile. The hepatic duct above the obstruction is distended (glass rod inserted); the common bile-duct is constricted below, only admitting a bristle. There are enlarged lymphatic glands around the common bile-duct which are stained with bile.

Microscopic section of liver: There is a monolobular cirrhosis. The bile-ducts are dilated. There are patches of round cells in places. There is also inspissated bile and a fairly extensive fatty degeneration.

Sequel to Supposed Case of "Idiopathic" Hepatic Cirrhosis with Recurrent Jaundice, shown on April 10, 1930: Report and Specimen.—F. PARKES WEBER, M.D.

The patient was a girl aged 12 years, when she was brought before the Section in 1930 by Dr. Parkes Weber and Dr. M. Scholtz (*Proceedings* of the Section, 1930, xxiii, p. 69). Afterwards she suffered from intermittent attacks of epigastric pain and sometimes vomiting. Ultimately the jaundice became very deep and persistent, with complete absence of urobilin and urobilinogen from the urine, showing that no bile was entering the duodenum. The abdomen became enormously distended, apparently by the liver, and yet this could not have been due to mere cirrhosis of any kind. There was likewise variable slight ascites for a time. She died on January 14, 1934, and the necropsy showed a relatively fine hobnailed cirrhosis of the liver and enormous so-called cystic dilatation of the common bile-duct. The immediate cause of death was evidently hæmorrhage into the peritoneal cavity and into the dilated duct from a slit-like perforation in the duct-wall.[1] The terminal portion of the common bile-duct was neither dilated nor stenosed, but had evidently been occluded by external pressure from the great (cyst-like) dilated portion of the duct.

The case will be published elsewhere in full. A somewhat analogous case of a girl, aged 6 years, with hepatic cirrhosis as well as cystic (congenital) dilatation of the common bile-duct, was described by Dr. W. G. Wyllie in 1925 (*Lancet*, 1925 (i), p. 1342), but there are other cases in the literature of the subject, which are analogous in this respect.

The PRESIDENT said that although he had not seen a dilated common duct in childhood, the condition reminded him of certain cases which had been reported recently of cystic dilatation of the common duct in adults. He had recently had such a case in which the common duct was distended to the size of a coconut, and on exploration the cystic and hepatic ducts were found to open into it by valvular orifices. The opening into the duodenum was represented by a mere puncture, and it was difficult to see how bile could find its way through such a minute opening. There was no jaundice however. An anastomosis between the dilated duct and the duodenum led to relief of symptoms, and the patient reported well one year later.

Two Cases of Mediastinal Tumour: for Diagnosis.—J. N. O'REILLY, B.M., M.R.C.P. (for DONALD PATERSON, M.D.).

(I) M. L., male, aged 2 years and 9 months. First brought to hospital at age of 11 months on account of stridor, which had then only recently begun. No physical signs were found. Mantoux reaction negative. A skiagram showed a mediastinal mass.

He was treated with 1,600 mgm.-hours radium bib without marked effect.

With the passage of time the stridor has diminished and is now slight. At no time has the child shown other symptoms referable to the mediastinum.

Radiological reports.—21.6.32. Enlargement of the mediastinal shadow, strongly suggestive of a mass of glands.

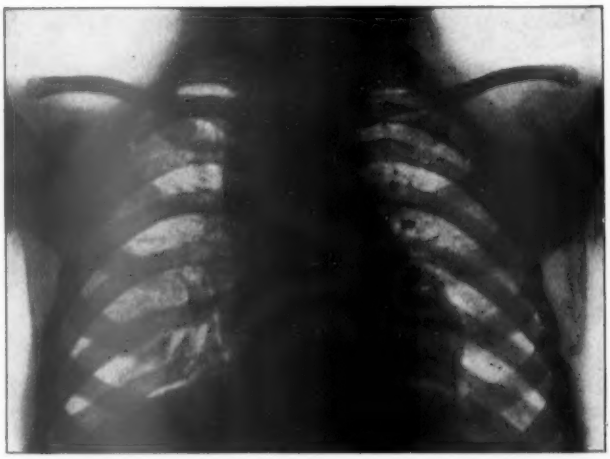
8.8.32. No alteration after radium treatment.

9.10.33. Unchanged. On the screen a mass is seen in the anterior mediastinum projecting a little into the right lung field.

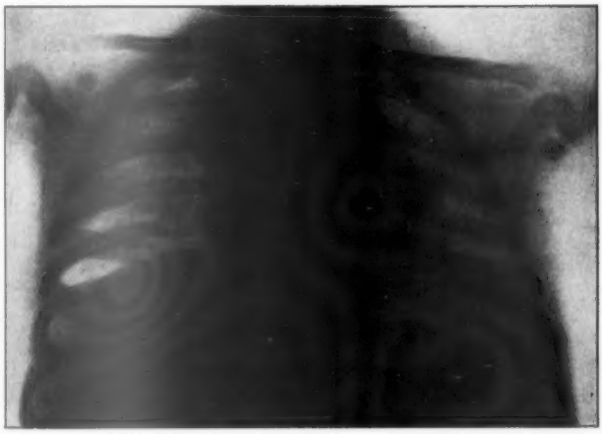
(II) D. B., aged 13 months. Sent up at age of 5 months on account of accidental discovery of a loud apical systolic murmur. Condition diagnosed clinically as congenital morbus cordis. No symptoms or marked physical signs.

[1] Mr. T. W. Lawrence finds that the perforation is due to colliquative degeneration of hyaline fibrous tissue in the wall. The specimen is now in the Royal College of Surgeons Museum.

Radiological reports.—29.9.33. Heart displaced slightly to the left. Large opaque shadow in right upper zone, appearing to come from mediastinum. Diagnosis: Mediastinal tumour. ? nature.



M. L. 17.2.34.

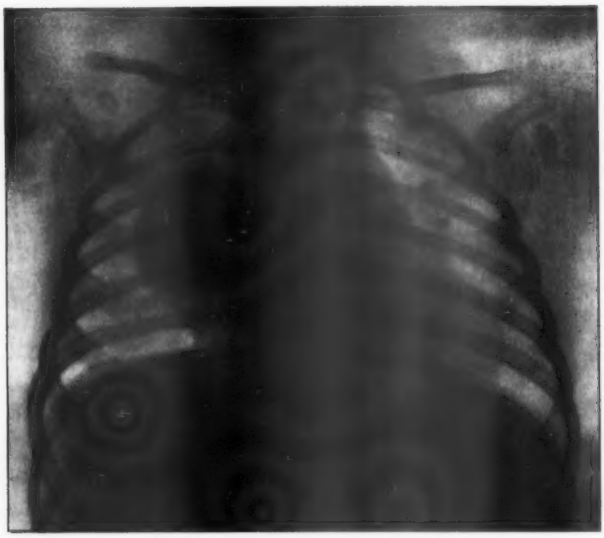


M. L. 18.6.32.

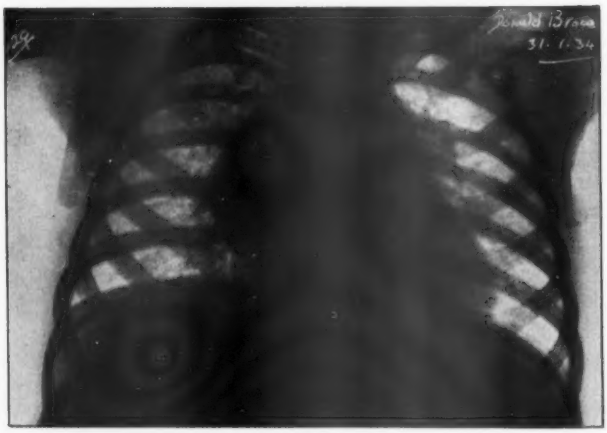
24.11.33. Shadow much smaller, and suggesting congenital morbus cordis.

1.2.34. Unchanged. Nature still doubtful.

The first diagnosis which suggests itself in these cases is that of enlarged thymus. The X-ray appearances, however, are against this. The thymus shadow does not extend down into the thorax or into the lung field.



D. B. 27.9.33.



D. B. 31.1.34.

It seems, therefore, more probable that these are cases of dermoid or teratoma. Teratoma is rare in infancy and childhood, although a number have been described. In view of the lack of symptoms there seems to be no indication for action in these cases and I propose to watch them.

Clinical Section

President—BERNARD MYERS, C.M.G., M.D.

[*March* 9, 1934]

Large Lymphangioma or Telangiectasis, occupying lower half of left Abdomen and left Leg.—W. A. MILLIGAN, M.D.

K. D., a male infant born in January 1925.

This case was shown at a meeting of the Section in January 1926[1] (when the child was one year old). Since then, the condition has remained very much the same, the leg growing in proportion to the body. There have been numerous attacks of fever, lasting several days, and then passing off, and there has been a considerable amount of pain in different parts of the leg, more especially the foot. The leg has become more sensitive during the last few years, and cold weather seems to have a direct relation to discomfort.

The most notable feature is that the foot has spread out very considerably; this fact is probably due to the patient having been walking on it much more lately than he used to do.

On the whole the general condition is not so good; the child has become more nervous and certainly less vigorous during the last year or two.

Mr. H. A. T. FAIRBANK said that he did not think it possible to amputate the leg, as the nævoid condition extended right up to the groin, and there was even a vascular swelling in the usual situation of an inguinal hernia. He could only suggest that deep X-ray therapy should be given a trial. He had recently seen a very similar case, but in that the nævoid condition faded off at the level of the knee and he was able to amputate through the thigh without difficulty. In another recent case, that of a baby, the arm was affected, but in that there was a minimum of nævus and a maximum of fibro-lipoma. Amputation was performed without trouble, a little below the shoulder. The bones in that case were honeycombed.

Yellow, thickened Nails.—BERNARD MYERS, C.M.G., M.D. (President).

John R., aged 37, married, one child. Patient states that during the last six months the nails of all his fingers and toes have become yellow, and that the condition is becoming worse. No pain, tenderness or discomfort of the digits.

Has suffered from dyspepsia for two years and eats no red meat. He takes cooked carrots about once weekly. Motions have been, he thinks, paler during the last two months than formerly. Urine does not stain linen.

Urine: normal; no bile.

Appetite poor; nausea after all food remains unless he takes an alkaline draught. Bowels open daily. Denies venereal disease. Suffers from winter cough. Was gassed in the war.

He is a pharmaceutical chemist but says that he does not take or handle drugs which might colour his nails. No similar case in family or at the pharmacy.

He is a well-made man and weighs 12 st. 6 lb. Heart normal; lungs, chronic bronchitis; abdomen, nothing abnormal, except possibly slight tenderness over the gall-bladder. Skin normal. Eyes normal. Some tobacco-stained teeth.

1 *Proceedings*, 1926, xix (Clin. Sect., 35).

All the nails of the fingers and toes are hypertrophied and moderately yellow. The fingers are more deeply stained than the toes. The colour seems evenly distributed on the nails, but the coloration and hypertrophy start from the nail beds. The nails of the thumbs and those of the big toes are more thickened than the other nails ; there are transverse ridges near the base.

An X-ray examination was made at St. Bartholomew's Hospital, February 24, 1933, but only gastro-duodenal irritability was found ; no ulceration. Gall-bladder normal.

Parkes Weber described various forms of leuconychia in *International Clinics*, vol. i, series 28-1918.[1] Knowsley Sibley in the *British Journal of Dermatology*, 1911, iii, xxiii, 281, described a case of a man, aged 23, who developed yellow, thickened nails a few years after being cured of syphilis. An iodide mixture was given and a salicyl ointment applied to the nails, which became quite normal again in colour and thickness.

Dr. PARKES WEBER said that in some respects the nails in this patient resembled those referred to, which in 1918 he had grouped together under the heading "incomplete leuconychia." In some of his (Dr. Weber's) cases the partial whiteness of the nails had been associated with more or less thickening ("scleronychia").

Essential Purpura Hæmorrhagica. (Previously shown October 1931.[2])—BERNARD MYERS, C.M.G., M.D.

Joyce M., aged 9 years, had splenectomy performed at the Royal Waterloo Hospital in July 1931 for acute essential purpura hæmorrhagica. In addition to the purpuric spots on the skin, continual oozing of blood occurred from the gums and both nostrils.

It was her first attack. No similar case in family.

The platelet count was 16,000 per c.mm. ; clotting time 7½ minutes (normal by method employed) ; capillary resistance test positive ; bleeding time over an hour. Wassermann reaction negative.

The symptoms became more and more severe but ceased within a few minutes of tying of splenic vessels.

The child has remained well since and no further hæmorrhages have occurred.

5.3.34.—Blood-count (Dr. Knott) : Red cells 4,720,000 ; Hb. 89% ; C.I. 0·94 ; white cells 9.200 (polys. 55·5% ; eosinos. 7·5% ; basos. 0·5% ; lymphos. 27·5% and hyals. 9%). Red cells show no significant abnormality. Platelets relatively numerous—152,000 per c.mm.

Gaucher's Disease. Splenectomy.—BERNARD MYERS, C.M.G., M.D.

Jean W., aged 5 years, has been shown before this Section previously.[3] She came to the Royal Waterloo Hospital two-and-half years ago with distinctly enlarged abdomen due to the great enlargement of the spleen and liver. There was a slight yellowish tinge on the skin. No pingueculæ present. Nutrition of skin and muscles poor. Spleen reached to pubis and liver nearly to umbilicus. Both were smooth and not tender. No fluid present in the peritoneal cavity.

There had been three attacks of epistaxis, the last being followed by vomiting of blood. Urine normal.

A full-time child, birth-weight 6¼ lb. ; walked when 18 months old. Abdomen first noted to be enlarged when 3 months old.

1 F. P. Weber, "Some pathological conditions of the nails," *Internat. Clinics*, Series 28, 1918, i, pp. 108-130. On p. 13 Dr. W. K. Sibley's case of a man, aged 23 years, with all his finger-nails and toe-nails coloured yellow and somewhat thickened, was referred to. In the course of thirteen months his nails all became practically normal again.

2 *Proceedings*, 1931, xxv, 154 (Clin. Sect., 26).

3 *Proceedings*, 1932, xxv, 396 (Clin. Sect., 30) ; 1933, xxvi, 360 (Clin. Sect., 30).

Parents healthy; one other child, younger, who enjoys perfect health. No similar case in family.

Blood examination on admission: Red cells 1,350,000; Hb. 19%; C.I. 0·7; white cells 2,200. (Polys. 44%; lymphos. 39%.) Van den Bergh reaction, negative direct and indirect. W.R. negative. Reds: fragility normal.

Splenectomy performed September 1931. Cells showed microscopically typical nests of Gaucher cells, replacing some of the normal splenic tissue.

Great general improvement since operation and the anæmia has disappeared. She is mentally normal and likes playing games with other children. About eighteen months ago she suffered from osteomyelitis of the right femur; Gaucher cells present in the discharge; perfect recovery. There is slight kyphosis in the mid-dorsal region.

Blood-count (23.2.34).—R.B.C. 4,400,000; Hb. 79%; C.I. 0·89; white cells, 19,000; platelets plentiful. Reds show no significant abnormality. No myelocytes.

Cushing's Basophil Pituitary Syndrome.—E. STOLKIND, M.D.

Female, aged 25, is suffering from hirsuties, high blood-pressure, attacks of dyspnœa and cough, headaches and migraine, mitral stenosis; obesity (limbs normal); polycythæmia. Clinoid processes approximated; albumin, granular and epithelial casts in urine; hair falling out.

Mother, who was not hairy, suffered from migraine and died from nephritis. Father and two brothers, healthy.

Patient had diphtheria at the age of 4, and rheumatic fever at the age of 12. At about 16 hair began to appear, first on the upper lip, and then spreading to the

face. At 17 it appeared also on the chest between the breasts, and later on the face, shoulders, extremities, etc.; the pubic hair spread as far as the umbilicus. The first menstrual period was at the age of 12 and subsequently has been regular, but during the last months it lasts two days less and she loses much less. She married in 1927 and has had three pregnancies: two premature births at six months at 21 and 22 years of age respectively, and a miscarriage of two months at 24; all without any obvious cause. She has suffered from headaches since she was 12, and more so since she was 15. They are mostly typical attacks of migraine with nausea and vomiting, visual disturbances (sees various colours), etc. She had also headaches without these symptoms.

Since August 1, 1933, there have been four attacks of dyspnœa (two severe) with difficult inspiration, coughing and frothy blood-tinged sputum. The first and fourth attacks occurred during coitus. Lately she complained of pain in the left side of the chest, left shoulder, and upper arm.

She is a dark, short, plethoric-looking, round-shouldered, fat woman; her height is 4 ft. 11½ in.; weight now 11 st. 2 lb. She says she was 10 st. 5 lb. in 1927; 13 st. in February 1932. The obesity is chiefly in the trunk, with pads of fat; the extremities are spared. She has a high colour. The skin is dry. Many small dark brown spots on the body. There are purplish striæ atrophicæ on the abdomen, back and thighs. Acrocyanosis of the legs with ecchymoses. Easily bruised. Now shaves her beard and moustache several times a week. Much hair between the breasts and an extension of the pubic hair upward to the umbilicus, a few hairs over areolæ round nipples, etc., on extremities and on the dorsum pedis. Lately she has noticed that the hair on the temples is falling out. Dr. F. G. McCann found the genital organs normal. She has mitral stenosis. Pulse, 90-120.

January 1933.—Albumin and a few granular and epithelial casts found.

August 1933.—Albumin in urine; blood-urea, 30 mgm. per 100 c.c.

Bilateral pyelography gave normal results.

During the last fourteen months blood-pressure 235-260 (systolic) and 150 (diastolic). Wassermann and Kahn reaction (blood) repeatedly negative.

Latest investigations.—X-ray (Dr. Martin Berry): Heart horizontal and enlarged. Sella turcica: clinoid processes rather approximated.

Nothing abnormal in the kidneys; no evidence of calcified tibial arteries.

Blood-count (Dr. Carnegie Dickson).—R.B.C. 6,150,000 per c.mm.; W.B.C. 14,200 per c.mm.; Hb. 102%; C.I. 0·83.

Differential leucocyte count (of 200 counted): Polys. 76%; lymphos. 17·5%; large monos. 4·0%; eosinos. 1·5%; basos. 0·5%. Films: Many R.B.C. 7 to 6½ μ, or a little less.

Urine (catheter specimen): Urea, 0·8%; albumin, 0·08% (Aufrecht); occasional degenerated cellular casts and a few epithelial cells, probably from collecting tubules and very occasional polymorphs. Total quantity of urine in twenty-four hours 1,200 c.c., sp. gr. 1010-1020.

Urea concentration test: resting, 1·3%; after one hour, 1·6% urea; after two hours, 75 c.c. urine and 1·7% urea. Blood-urea, 68 mgm. per 100 c.c. Urea concentration factor, 19·1.

Blood-sugar test: fasting, 0·106%, it rose after 50 grm. of glucose to 0·181% in one hour, and 0·135% in two hours; in urine 0·12% of sugar after two hours. In this case the adrenal cortex, in all probability, is also affected.

Fundi (A. Sorsby). Marked arteriosclerosis (crushing). Right: occlusion of a peripheral arteriole on temporal side; new vessel formation. Left: hæmorrhages and exudates which are absorbing.

This is a case of Cushing's pituitary basophil syndrome. The final proof of this diagnosis in cases with normal pituitary fossa is so far only possible after examination of serial sections of the pituitary gland. There are no special pathognomonic symptoms

or signs of Cushing's pituitary basophil syndrome, which would distinguish it from a genito-adrenal syndrome.

Dr. J. H. Douglas Webster is giving a short course of deep X-ray treatment to the pituitary gland of my patient.

I am indebted to Dr. W. R. Reynell for facilities to investigate this case.

Two Cases of Dyspituitarism.—D. C. HARE, C.B.E., M.D.

(I) *Cushing's basophil pituitary syndrome.*

Chief symptoms and signs.—Attacks of severe headache and vomiting. Persistent metrorrhagia. Hirsutism, male type, with loss of scalp hair. Skin of face greasy with acne eruption. Adiposity of face, neck, shoulders, and trunk. Limbs normal. Kyphosis. Polycythæmia with cyanosed extremities. Raised blood-pressure. Pituitary fossa not enlarged.

History.—Miss R. L., aged 32, machinist. In good health till November 1931, when she missed two menstrual periods and began to be languid and sleepless. After an attack of tonsillitis in February 1932 the menses became gradually prolonged lasting up to six weeks. The daily loss was not excessive at any time; during 1933 the average duration was from seventeen to twenty-one days with irregular intervals.

FIG. 1.—Miss R. L. at age 24.

FIG. 2.—At age 32.

Changes in appearance were noticed early in 1933. Gain in weight about half a stone; the complexion, previously good, became spotty, the scalp hair broke off short, and the beard began to grow in April 1933. Headaches, to which she was always liable, increased in frequency, severity and duration, vomiting was liable to occur on waking or would follow the development of the headache. The appetite was very good but not excessive. Thirst increased and nocturnal frequency of micturition increased. Voice, no change noted. No history of hæmorrhages or bruising obtained except a slight hæmoptysis in January 1934. Mentality and efficiency unimpaired; patient continued at work until February 1934.

Past and family history.—Patient is the tenth of twelve children. She has had no previous illnesses of importance. Menses previously regular. Family healthy.

Examination.—Appearance: The patient is a small woman, height 5 ft. 2 in., florid, with rounded shoulders, short thick neck and double chin. The face and extremities are congested and the lips a deep colour. The skin over forehead and cheeks is thick and coarse, with few creases; it is greasy, and comedones and acne eruption are present. Hair: The scalp hair is short, thin, curly and brittle and makes hardly any growth, the eyebrows are thick and rather coarse; below the chin is a short thick growth of beard (clipped about once a week), there is a slight growth only in the whisker and moustache areas. There is a line of hair from pubes to umbilicus, sparse hairs round the nipples, no excess of hair on limbs or trunk elsewhere. Distribution of adipose tissue: This is chiefly on the lower part of the face, neck and shoulders. There is moderate obesity of the abdomen. No striæ atrophicæ present. The limbs, hands and feet are slender. Breasts small. Circulatory system: the heart is moderately enlarged, action forcible, sounds clear. Blood-pressure, systolic from 190 to 196, diastolic from 130 to 144, when up and about, lower when at rest. Electrocardiogram shows marked left side preponderance and suggests some myocardial damage. Abdomen: Liver, spleen and kidneys not palpable. Genitalia: The labia are normal; there is slight enlargement of the clitoris. Cervix small and soft. Uterus not defined. Left ovary enlarged. (Professor McIlroy's report.) Eyes: Fundi normal, fields of vision and blind spot normal. Other systems: Lungs, urinary and central nervous systems nil.

Special investigations.—Blood examination: R.B.C. 7,620,000 per c.mm.; Hb. 126%; C.I. 0·8; W.B.C. 16,000 per c.mm. *Differential:* Polys. 85; basos. 0·5; eosinos. 0·5; monos. 4·5; large lymphos. 5; small lymphos. 4·5. X-ray examination; Pituitary fossa, rather smaller than normal; Antero-posterior diameter 11 mm.

Kidneys and suprarenals (by intravenous pyelogram), outlines appear normal.

Biochemical investigations (Dr. Pillman Williams).—Carbohydrate metabolism: No urinary sugar found on ordinary diet. Resting blood-sugar normal; after 100 grm. glucose, maximum rise, at one hour 0·235%; at two hours, 0·115%. Urine sugar, corresponding traces only at one hour and two hours.

Insulin sensitivity test: Resting blood-sugar 0·089%; 10 units of insulin given. At half an hour 0·062%, at one hour 0·062%, at one and a half hours 0·071%.

Basal metabolic rate: Plus 34%, R.Q. 0·8.

Calcium metabolism: Blood-calcium, two estimations, 9·45 mgm., 10·9 mgm. Skiagram of long bone with control shows no lack of lime salts.

Urine examination for prolan A (Professor Webb): Trace only, not more than in normal urine, male or female. Urine: No albumin, no casts. Urea concentration test: Normal.

Blood-chemistry.—Urea (two examinations) 38 mgm.%; 39 mgm.%; non-protein nitrogen 37·7 mgm.%.

Ratio: $\frac{\text{Urea}}{\text{N.P.N.}} = 48{\cdot}3$. Phosphorus 2·32 mgm. %. Phosphatase 0·148 units. Cholesterol 161·3 mgm. %. Wassermann reaction, negative.

Comment.—(i) As in other reported cases, there is no enlargement of the pituitary fossa or other direct evidence of tumour. The patient suffers from prostrating headaches with vomiting but these do not appear to be due to increased intracranial pressure. (ii) An unusual symptom is the absence of amenorrhœa except for two months at the outset; instead there is very prolonged menstrual loss up to six weeks. (iii) It is proposed to treat the patient with X-rays applied to the pituitary fossa.

(II) *Pituitary Tumour (Chromophobe Adenoma) with Polyglandular Deficiencies. (Thyroid, Suprarenal, Pancreas.)*

Chief Symptoms and Signs.—(i) Thyroid deficiency. Extraordinary lethargy, slow blurred speech, slow reactions, intelligence normal. Skin pallid, shiny and dry,

eyelids puffy, lips thickened. Anæmia secondary type. Basal metabolic rate minus 38·5%. (ii) Suprarenal deficiency. Clinical signs of Addison's disease. Brown pigmentation of tongue and buccal mucous membrane. Blood-pressure: systolic 90-100, diastolic 64-70. (iii) Pancreatic deficiency. Clinical diabetes. Admitted January 1934, with ketosis, blood-sugar 0·356%. Now controlled by insulin 48 units, and diet with CH 200 grm. (iv) Pituitary tumour. No neighbourhood symptoms. Pituitary fossa very large, clinoid processes thinned out.

History.—Mrs. E. S., aged 47, housewife. Was perfectly well until an attack of "influenza" in February 1927. This illness was a short febrile attack with violent headaches. Two months later she noted the gradual onset of symptoms with which she was admitted to hospital in December 1927. She complained then of lassitude, depression, flatulent indigestion, gain of weight, thirst and constipation. The menses were regular but scanty. She was then noted to be fat and flabby, with normal distribution of fat. Weight 11 st. 13 lb. There was at that time secondary anæmia, pigmentation in the mouth, normal blood-pressure, basal metabolic rate minus 20, a mild diabetes easily controlled by diet.

In January 1934 patient was readmitted to the hospital, having been lost sight of in the meantime. She complained of extreme weakness, and lethargy, there was severe ketosis and diabetes. She had lost 3 st. in weight, but was fairly well till two years ago.

Personal and family history.—Patient is one of twin children, the other died in infancy. She has three children; last pregnancy in 1921. Menses regular till May 1933, when they ceased. Was very energetic before present illness.

On examination.—Patient is a small dark-haired woman with the clinical appearance of myxœdema, as noted above. The skin is pallid and yellowish; no abnormal pigmentation noted except in the mouth. The lips are thick and prominent, the tongue papillæ normal. Pigmentation: There is diffuse brown pigmentation along the right border of the tongue, and well-defined patches on the mucous membrane on both sides. Circulatory system: The heart appears normal. The blood-pressures are persistently low. Lungs, abdomen: Nothing abnormal. Central nervous system: Evidence of peripheral neuritis of legs. Tenderness of muscles, loss of reflexes. No other abnormality. Eyes: Left convergent squint since childhood. Fundi normal, fields of vision normal "no evidence of pituitary dysfunction" (Miss Ida Mann.)

Investigations made in 1927 *and* 1934, *compared.*

Pituitary fossa: In 1927: Very large, 18 mm. in antero-posterior diameter. Clinoid processes thinned out. In 1934: No change, clinoid processes appear less defined.

Basal metabolic rate: In 1927 minus 20%. In 1934 minus 38·5%.

Blood examination: In 1927 R.B.C. 3,360,000; Hb. 54%; W.B.C. 6,800 per c.mm. In 1934 R.B.C. 4,480,000; Hb. 74%; W.B.C. 7,400 per c.mm.

Pigmentation: No apparent change.

Blood-pressure: In 1927 systolic 115; diastolic 80. In 1934 systolic 90 to 100; diastolic 64 to 70.

Carbohydrate metabolism: In 1927: Urine, sugar occasionally, easily controlled by diet. Blood-sugar curve after 100 grm. glucose. Fasting 0·152% very high rise to maximum of 0·462% at 2 hours. Urine sugar corresponding 2·67%. In 1934: Admitted with ketosis and blood-sugar of 0·356%. Required insulin 60 units with diet of 200 grm. CH. Later insulin 48 units.

Insulin sensitivity: Insulin 20 units and breakfast: at three hours blood-sugar 0·133%; four hours 0·071%; five hours 0·071%.

Other recent investigations.—Blood-urea January 29, 1934, 29 mgm. %. February 1, 41 mgm. %. Fractional test meal. Free acid present in later specimens. Much mucus in earlier specimens, with no free acid.

Comment.—(i) The evidence that the group of glandular deficiencies in this patient is to be attributed to pituitary dysfunction rests on the finding of the enlarged pituitary fossa. (ii) The absence of history of menstrual irregularity is unusual, the cessation of menses a year ago is probably an early menopause. (iii) The patient has been treated with a high salt diet without apparent result. She is now taking thyroid and is improving. Professor Woollard states that the atrophy of the adrenal which follows pituitary ablation is not counteracted by cortical extract. No cortical extract has as yet been given in this case.

Dr. F. PARKES WEBER said he agreed that Dr. Hare's first case was an example of Cushing's pituitary syndrome. Nevertheless, the patient had neither cutaneous "striæ" nor the remarkable purpuric erythematous dystrophic condition of the skin of the legs which had been a striking feature in the most typical cases. The excess of facial hair and the thinning of the scalp hair (with a tendency to acne, perhaps) suggested, it should be noted, a suprarenal cortical ("interrenal") syndrome.

Dr. Stolkind's case might be a less advanced example of Cushing's syndrome, but the most urgent feature was doubtless the high blood-pressure with chronic renal disease.

Dr. Weber agreed with Dr. Hare's explanation of her second case, but suggested that perhaps the patient's thick lips might be due not to thyroidal deficiency but to overactivity of the eosinophil cells of the anterior pituitary lobe.

Basicranial Neoplasm with Multiple Cranial Nerve Paralyses: Apparent Cure by Deep X-ray Therapy.—WALTER M. LEVITT, M.D., and R. F. PHILLIPS, F.R.C.S. (by permission of Dr. HINDS HOWELL).

A. J. C., aged 52. First seen 16.11.32, complaining of attacks of stabbing pain in left side of face, with nasal catarrh and recurrent epistaxis, for ten months. Numbness of left side of face and tongue, and deafness in left ear for two months. Had lost much weight. The pain was so severe when he was first seen that the patient was unable to move head.

On examination.—Thin, pale man. Cranial nerves: 1, 2, 3 and 4 normal; 5th, diminished sensation in skin, and deafness on left side; 6th, 7th, 8th normal: 9th and 10th, anæsthesia of left side of face and tongue, and immobility of left side of tongue and palate. Sanious discharge from left post-nasal space: palate and uvula much swollen; appearance as if produced by a massive neoplasm behind. Middle-ear type of deafness on left side. Cervical glands palpable on both sides, more so on left side than on right. Skiagrams showed sphenoidal sinus opaque; left antrum dark; no bone destruction.

Deep X-ray therapy, 16.11.32 to 13.12.32.—Patient improved steadily from the beginning of treatment, and pain and deafness slowly diminished. He is now free from pain, and can hear well, but complains of sleepiness. He has gained much weight since the treatment.

Plasmoma of Sacrum: Apparent Cure by Deep X-ray Therapy.—WALTER M. LEVITT, M.D., and R. F. PHILLIPS, F.R.C.S. (by permission of Sir CHARLES GORDON-WATSON).

B. W., aged 46.

History: Patient first noticed pain in the right buttock and back of thigh in July 1931. In November 1931, and again in January 1932, he had attacks of retention of urine, and on the latter occasion was admitted to the Metropolitan Hospital. A diagnosis of sarcoma of the right half of the sacrum was made, and Mr. McNeill Love inserted radium; microscopical examination shows the tumour to be composed entirely of plasma cells, some of which are in mitotic division. Following the radium treatment, there was some temporary improvement, but when the tumour again began to enlarge the patient was transferred to St. Bartholomew's Hospital.

August 1932: Pulsating tumour over right half of sacrum 8 × 6 × 3 cm. Deep X-ray therapy given by the intensive split-dose method; 200 kv., 4 ma., 1·5 mm. cu. filtration; three fields: (i) anterior; (ii) right posterior glance; (iii) left posterior glance; total dose 1,400 *r* to each field over three weeks.

Progress: Symptoms disappeared while under treatment. Tumour disappeared in two months. Skiagrams show progressive reformation of sacrum.

Remarks: The solitary plasmocytoma is to be regarded as a distinct entity. It is locally destructive but does not metastasize. Its vascularity often prevents successful excision, but its radiosensitivity renders its treatment by modern high-voltage X-rays the method of choice.

Carcinoma of Œsophagus: Disappearance of Growth after Deep X-ray Therapy; ? Damage to Lungs by X-rays.—WALTER M. LEVITT, M.D. and R. F. PHILLIPS, F.R.C.S. (by permission of Mr. BEDFORD RUSSELL).

A. L., aged 40.

First seen 29.8.33, with a history of progressive difficulty in swallowing, regurgitation of food, and pain in lower chest, for two months; could swallow only liquids; had lost several pounds in weight.

Radiographic investigation showed the appearance of a carcinomatous stricture in the middle and lower thirds of the œsophagus.

Œsophagoscopy revealed a typical ulcerated growth of the œsophagus. Microscopical examination suggested epithelioma but was not conclusive.

High-voltage X-ray therapy 29.8.33 to 26.10.33. By the end of the treatment, swallowing was greatly improved, and skiagrams showed an apparently normal œsophagus. Patient gained over a stone in weight.

Three weeks after the treatment, patient began to complain of cough and dyspnœa on exertion, which became steadily worse for about two months, and has remained stationary ever since.

Skiagrams taken showed no changes in the lungs until a week ago, when evidence of early fibrosis was observed. The fibrosis is regarded as having been produced by the X-ray treatment.

Nodal Rhythm.—B. T. PARSONS-SMITH, M.D.

P. W., male, aged 62. Admitted to hospital May 1932, complaining of attacks of giddiness and breathlessness on exertion during the previous six months. Examination findings: Heart enlarged to the left, hypertrophy of left ventricle (confirmed by X-rays); rhythm an irregular bradycardia, 36-60; blood-pressure, 110/70; vessels moderately thickened for age; Wassermann reaction negative. Electrocardiogram: curves indicative of a shifting pace-maker and partial sino-auricular block; barium chloride (½ gr. t.d.s.) prescribed, and ephedrine hydrochloride (½ gr.) for the attacks of giddiness; symptoms relieved by the treatment, the bradycardia persisting; electrocardiogram (10.5.33) curves typical of nodal rhythm, rate 42; patient still at business and relatively free from symptoms.

At routine examination, January 17, 1934, patient was *in statu quo ante* subjectively, but heart-rate was 120, and electrocardiogram was typical of an irregular auricular flutter.

Patient admitted to hospital 3.2.34; digoxin prescribed, one tabloid (0·25 mgm.) t.d.s. for three days, the dose then being doubled and continued (0·50 mgm. t.d.s.) for four days, when auricular fibrillation developed and the drug was discontinued.

Reversion to nodal rhythm the following day, the transition being characterized by irregular periods of asystole associated with sensations of giddiness and transient syncopal seizures.

Later recovery uneventful.

[Dr. Parsons-Smith briefly summarized the outstanding features of the case: he regarded the condition as one of widespread myocardial degeneration which had involved the lower and the upper chambers of the heart, incidentally also the region of the normal pacemaker; he showed electrocardiograms illustrative of the varying vicissitudes of rhythm which had developed in consequence; he referred to the possible advantages and contra-indications of barium chloride therapy in such a case and he emphasized the prompt reversion from auricular flutter which the prescription of digoxin had effected.]

Dr. POYNTON said that members might like to hear of a boy who had from birth every kind of cardiac irregularity with repeated attacks of cyanosis and even fits of unconsciousness. Even at four months of age his heart was acutely dilated and he was admitted to hospital apparently moribund.[1] Cardiologists had agreed that the basal fault was auricular flutter. He (Dr. Poynton) had seen this boy again at the age of seven years. He was at school, leading a normal life, and no attack had occurred for at least a year.

Abdominal Tumour.—NORMAN HILL, M.D.

G. T., aged 20, male, was admitted to hospital 28.12.33, complaining of abdominal pain and vomiting, of one week's duration. Bowels regular, no loss of weight, no cough. The symptoms were relieved after a few days' rest in bed and light diet. He never looked ill, neither did he complain of anything after the abatement of his initial symptoms.

Examination revealed a large hard tumour occupying the left hypochondrium, and the left lumbar, left inguinal and left hypogastric regions, and feeling not unlike an enlarged spleen; there was no œdema of the legs or abdominal wall, and no varicocele; the tumour was not tender. Previous to this examination the patient had been unaware of any abnormality in his abdomen.

He remained in hospital until 17.2.34, during which time the tumour appeared to shrink somewhat in size, and has certainly altered in position, as it now occupies the lower abdomen, right lumbar, and right hypochrondric regions. It is still extremely hard, and practically immobile. The patient gained 4 lb. in weight whilst in hospital.

In September 1931 he had had a similar attack of pain and vomiting which lasted forty-eight hours, and for which he was admitted to Whipps Cross Hospital; he remained there for a fortnight under observation as a "? appendix case," and no abdominal tumour was felt there at any time.

Blood-count.—R.B.C. 5,250,000; Hb. 100%; C.I. 0·95; W.B.C. 10,000; polys. 74%; lymphos. 21%; large monos. 2%; eosinos. 3%. Wassermann reaction negative. Blood-urea 30 mgm.

Pyelography normal. Skiagram, barium meal and enema normal; pelvic bones normal.

Dr. PARKES WEBER said that the abdominal swelling might be due to a retroperitoneal fibro-lipoma or to a cyst of some kind, but the rapid increase in size was against the diagnosis of the former.

Postscript.—At operation the tumour was found to be a pure fibroma, but owing to its being adherent to the gut, it was irremovable.—[N.H.]

Hepatosplenomegaly with Mental Deficiency and Bone Changes.—R. W. B. ELLIS, M.D. (by permission of HUGH THURSFIELD, M.D.).

G. R., male, aged 3 years and 5 months; full term, normal delivery, birth-weight 8¼ lb.; no illnesses except upper respiratory infections; has never been jaundiced. Abdomen and head noticed to be abnormally large since early infancy.

February 1933.—Admitted to hospital at the age of 2 years and 3 months, on

[1] *Lancet*, 1927.

account of enlarged tonsils; spleen palpable three fingerbreadths, and liver two fingerbreadths, below costal margin. Weight 28 lb.; head circumference 20½ in. (normal 19 in.).

Blood examination (27.1.33).—R.B.C. 4,880,000 per c.mm.; W.B.C. 4,200; Hb. 74%; C.I. 0·75. *Differential*: Polys. 38%; lymphos. 57%; monos. 1%; eosinos. 1%; basos. 1%; myelos. 1%; metamyelos. 1%; reticulos. 1·6%. Fragility of red cells: incomplete hæmolysis in 0·30%; trace in 0·39%. Wassermann reaction negative.

FIG. 1.—G. R. showing heavy features, bushy eyebrows, and hepatosplenomegaly.

Family history.—Mother and father alive and well, and unrelated; father said to have been rachitic with "large head" during childhood. One younger child (a boy) died in the Hospital for Sick Children, aged 10 months, with enlargement of liver and spleen, cerebral hæmorrhage, and hydrocephalus. The last blood-count before death (29.9.32) showed R.B.C. 2,500,000 per c.mm.; W.B.C. 8,000; Hb. 50%; C.I. 1·0; polys. 23%; lymphos. 56%; monos. 10%; eosinos. 3%; basos. 2%;

myeloblasts 1% ; myelos. 4% ; metamyelos. 1%. 8 megaloblasts and 3 normoblasts per 100 W.B.C. Wassermann reaction negative. A diagnosis of von Jaksch's anæmia was made. At post-mortem examination the liver weighed 420 grm., and the liver cells showed extreme degeneration, partly fatty. The spleen weighed 125 grm. No cirrhosis of liver or spleen.

No other pregnancies. No other relatives known to be affected.

On examination.—An active, well-grown child, weighing 35 lb. Height 35¼ in. Circumference of head, 21¼ in. (normal 19½), chest (mid-expansion) 23½ in., abdomen (umbilical level) 28 in. Mental development retarded, though child can play, and attention can be attracted readily. He can walk alone, but does not talk and makes no attempt to control excreta. A peculiar appearance is given to the face by the massive skull and heavy features. There is marked frontal bossing, and less marked parietal and temporal bossing, the latter causing widening in the bi-temporal

FIG. 2.—G. R. skull: showing bossing, vessel markings and patent coronal suture. Sella turcica not markedly affected.

diameter. Intermeatal measurement (over vertex) 14½ in. (normal 12). The anterior fontanelle is not palpable, and there is flattening of the skull in this region. The skin has a slightly muddy tint, though the boy does not appear pale and is not jaundiced. The hands and feet are of normal size, but there is limitation of extension of the terminal phalanges of all the fingers, and definite incurving of the little fingers of both hands. The abdomen is large, with eversion of the umbilicus. The liver is enlarged five fingerbreadths below the costal margin and the spleen three fingerbreadths ; both feel firm and smooth. The right testicle is in the scrotum, the left cannot be felt. Eyes normal. Teeth : upper incisors have been extracted ; otherwise normal. Hair of head and eyebrows is coarser and drier than normal for this age.

Skiagrams of the limbs show no changes. The skull shows unusually prominent vessel markings in the frontal area, and the coronal suture is open. The sella turcica appears, if anything, a little wider and deeper than normal, but there is no erosion.

Urine normal.

Blood examination (8.2.34).—R.B.C. 3,880,000; W.B.C. 9,650; Hb. 72%; C.I. 0·92; polys. 38%; lymphos. 50%; monos. 11%; myelos. 1%; reticulos. 8%.

Biochemical investigations (Dr. Payne):—

Adrenaline Test (normal rise—over 0·03%).

Fasting blood-sugar	0·086%
4 min. adrenaline given.	
Blood-sugar ¼ hr. after	0·107
„ „ ½ hr. „	0·102
„ „ ¾ hr. „	0·105
„ „ 1 hr. „	0·108

Lævulose Test (normal rise—less than 0·03%).

Fasting blood-sugar	0·092%
20 grams lævulose given.	
Blood-sugar ½ hr. after	0·098
„ „ 1 hr. „	0·103
„ „ 1½ hr. „	0·093
„ „ 2 hr. „	0·093

Van den Bergh reaction: Direct and indirect—negative.

Fragility of R.B.C. (1.3.34): Hæmolysis complete in 0·30% NaCl. Trace in 0·45%.

Inorganic blood phosphorus: 3·27 mgm. % (normal 4 to 5·5). Serum calcium 9·4 mgm. (normal 9 to 11).

Phosphatase: 12·4 units (normal for age 5 to 15).

Blood-urea: 29 mgm. %.

Plasma proteins: fibrin 0·35%; albumin 3·96%; globulin 2·19%.

Hepatosplenomegaly with Mental Deficiency and Bone Changes.—F. J. Poynton, M.D., R. C. Lightwood, M.D., and R. W. B. Ellis, M.D.

M. J., female, aged 4 years and 5 months. Two older children, aged 16 and 12, are well; parents unrelated; both well. One older child died, aged 9 months, with hydrocephalus. This child was born in British Guiana, where she lived for three years. Breech delivery; birth weight 7½ lb. Thought to have been well until 2 years old, when she began to have recurrent attacks of pyrexia, and during the subsequent six months the abdomen began to enlarge. Enlarged spleen and liver noted by doctor who examined her at age of 2½. She began to walk at 14 months, but is still extremely slow and uncertain in her gait. Cut first teeth at 10 months. teeth decaying rapidly after eruption. She has had snuffles since birth, but no rash. When 3 years old she was brought to England and admitted to the Hospital for Sick Children under Dr. Poynton (September 1932).

At this time she weighed 31½ lb.; head circumference 20½ in. The most remarkable feature was the facial expression, due to the heavy features, thick lips, depressed nasal bridge, and great frontal bossing of the skull. In addition, the skull showed some central ridging suggestive of oxycephaly, and the frontal veins were dilated. The abdomen was greatly distended, with eversion of the umbilicus; the spleen was enlarged three fingerbreadths and the liver a handbreadth below the costal margin. There was dorsal kyphosis, seen by X-ray examination to be due to deformed, wedge-shaped vertebræ. The teeth were widely spaced and defectively calcified. Both corneæ were hazy and covered with specks rather resembling

inflammatory keratic precipitates, but were thought by Mr. G. G. Penman to be in the cornea and in the nature of a congenital defect. The hair was dry and thin.

The blood was examined for filariæ and malarial parasites with negative result. Wassermann reaction negative. Stool examination showed no ova or parasites.

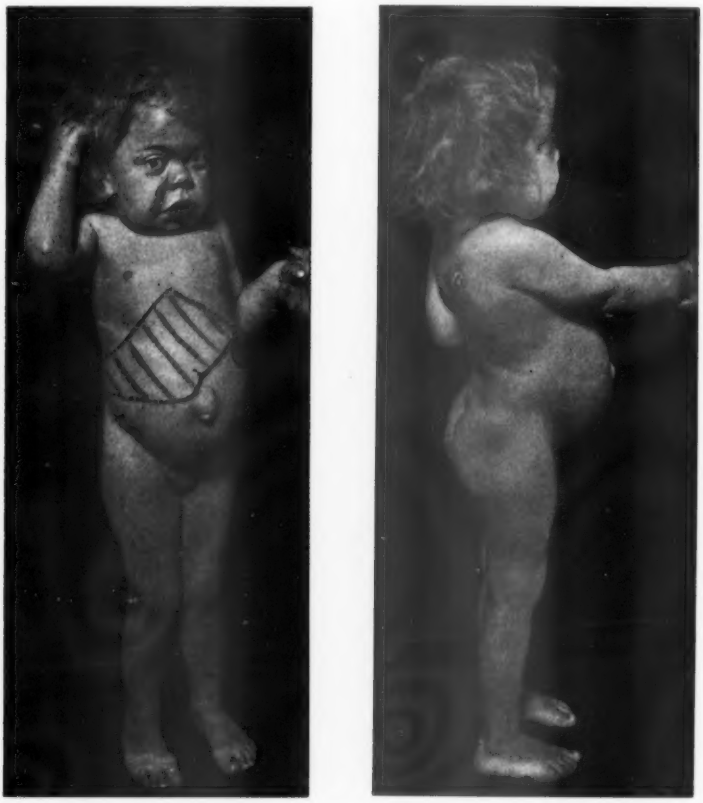


FIG. 1.

Blood-count (14.11.32).—R.B.C. 4,280,000 per c.mm.; W.B.C. 8,000; Hb. 85%; polys. 43%: lymphos. 49%; monos. 4%; eosinos. 1%; basos. 2%; Turck cells 1%.

Since this time, there has been little change in her general condition except that she appears stronger and has been free from pyrexia. She is still very backward mentally, speaking a few words only, and not having learnt to be dry or clean.

9.3.34.—Height 38 in. Weight 36½ lb. Head circumference 28⅛ in. Intermeatal measurement (over vertex) 13¼ in. Circumference of chest (mid-expansion) 21 in., abdomen (umbilical level) 23 in. The liver extends to the umbilicus; the spleen is palpable three fingerbreadths below the costal margin. There is some flaring of the lower ribs. The hands are rather short and broad, and show limitation of full

extension of the phalanges (more marked on left). There is fine down over the back and extremities; the eyebrows are thick and coarse.

Blood-count (12.3.34).—R.B.C. 4,926,000; W.B.C. 7,300; Hb. 90%; C.I. 0·91; polys. 47%; large lymphos. 28%; small lymphos. 17%; monos. 7%; eosinos. 1%.

Urine: Nothing abnormal found.

Radiological examination (Dr. Shires).—Skull (fig. 2): Bossing; tower shape; widely expanded sella turcica; thickening of base, especially left temporal. Right shoulder: Poorly developed glenoid. General expansion of ribs. Not much change in humerus. Hips: Poor development of acetabula. Coxa valga. Wrist: Expansion of radius, ulna, metacarpals and phalanges. Delayed growth of ossific centres. "Appearance of a dyschondroplasia."

FIG. 2.

Biochemical investigations (Dr. Payne): Blood-urea, 23 mgm. %. Blood cholesterol, 212 mgm. %. Blood phosphorus, 3·5 mgm. %. Serum calcium, 9·4 mgm. %. Plasma phosphatase, 8·5 units. Albumin, 4·05 %. Globulin, 1·59 %. Fibrin, 0·37 %. Total protein, 6·01 %.

Van den Bergh reaction: Direct and indirect, negative. Fragility of R.B.C.: Complete hæmolysis, 0·30%; trace of hæmolysis, 0·42%.

Lævulose tolerance test.

Fasting blood-sugar	0·084%
½ hr. after lævulose	0·092%
1 hr. „ „	0·110%
1½ hr. „ „	0·105%
2 hr. „ „	0·111%

Discussion.—Dr. R. W. B. ELLIS said that these two cases had features in common with a case shown by Dr. W. Sheldon at the last meeting of the Section for the Study of Disease

in Children which suggested that the three were examples of one disease entity.[1] All three were characterized by considerable enlargement of the liver and spleen, dating from early infancy, by a peculiarly heavy unchildlike facies, and by mental deficiency. In addition there were more or less pronounced bone changes; all three children showed very marked frontal bossing, the skulls of the two boys being abnormally wide, whilst that of the girl (Dr. Poynton's case) showed some degree of towering. There was possibly slight hypertelorism in each instance. Dr. Sheldon's and Dr. Poynton's patients had a very widely expanded sella turcica. The two cases shown at this meeting had not the same abnormalities of the long bones as were seen in Dr. Sheldon's case, but the girl had poor development of the right glenoid and of the acetabula, and deformities of the bodies of the lumbar vertebræ (particularly the second). Minor similarities were the thick, coarse eyebrows, and (to-day's cases) limitation of extension of the phalanges. Blood examination did not show any characteristic changes, though it was of interest that a younger brother of G. R. had died with a large liver and spleen, and a blood picture that had suggested the diagnosis of von Jaksch's anæmia. It was possible that the disturbance was primarily hepatic, although there was little biochemical evidence of hepatic dysfunction; the widely expanded sella turcica in two cases, however, suggested that there was at least some secondary abnormality of the pituitary.

Dr. POYNTON said that these cases might possibly represent a new clinical syndrome. His first thought had been of congenital syphilis, but none of the three cases supported that view, and in his case, not only the child, but also the mother had a negative Wassermann reaction. Both anti-malarial as well as anti-luetic treatment had been tried with no obvious results. He had come to the conclusion that this was a congenital syndrome of a most unusual type. The pituitary fossa in the girl's case was distinctly larger than normal.

Dr. PARKES WEBER said that several developmental diseases were to be thought of in which abnormalities in the development of the skeleton, notably of the head, were associated with enlargement of the spleen and more or less anæmia. These children constituted perhaps a new type. Another type was Cooley's "erythroblastic anæmia" in certain Italian families in North America. A type somewhat resembling the preceding one had been shown to him recently in England (an unpublished case).[2]

[The report of other cases shown at this meeting will be published in the next issue of the PROCEEDINGS *of the Section.]*

[1] *Proceedings*, 1934, xxvii, 1003 (Sect. Dis. in Child.)

[2] Dr. E. Wittkower reminded Dr. Weber of children with developmental "marble bones." These might represent yet another type. Dr. Weber did not mean to suggest that these types were really related to each other.

Section of Dermatology

President—HENRY MACCORMAC, C.B.E., M.D.

[*March* 15, 1934]

Pustular Psoriasis of the Extremities.—H. W. BARBER, M.B.

R. B., aged 26. The clinical features of this condition are well known to members of this Section, namely:—

(1) Reddish patches, covered by a varying degree of parakeratotic scaliness, and situated, as a rule symmetrically, on the thenar and hypothenar eminences and on the central parts of the soles.

(2) Intra-epidermic pustules, or vesicles, which become purulent, and the characteristic brownish "scabs" which result from the desiccation of these. These are for the most part formed in the patches, but may arise singly and discretely in normal areas of skin.

My patient illustrates these points very well. In his case the eruption has been present for about three years; it appeared first on the hands. The distribution is characteristic. On the hands the parts chiefly affected are the thenar and hypothenar eminences, but there is also a patch on the tip of the left little finger. On the feet, the central parts of the soles are involved, and also the left heel. There are no patches of the ordinary form of psoriasis elsewhere, nor are the nails affected, as they so often are in these cases.

I have shown this case because of a letter recently received from Dr. Clinton Andrews of New York, in which he asks whether I have had any beneficial results in the treatment of pustular psoriasis of the extremities by the removal of focal infection. He says that Dr. Birkman and he have reported a series of cases in which some were apparently cured by such treatment.[1]

The patient shown to-day had a very severe attack of tonsillitis seven years ago, and has had sore throats periodically ever since. His tonsils are obviously septic, and their appearances are those which, in my opinion, demand enucleation, in contradistinction to the simple hypertrophy often met with in children, for which operation is as a rule unnecessary and, in fact, contra-indicated.

He is at present in my ward at Guy's Hospital and the tonsils will be enucleated. I hope to report later to the Section whether the operation is followed by disappearance of the eruption.

I do not suggest that all these cases have infected tonsils: in many there is no evidence of it. Probably, in some, focal infection elsewhere may be the causative factor. I have just had reports from two patients:—

One, the first in which association of this condition with tonsillar sepsis was suspected, had had the eruption severely on the hands and feet from October 1927, to November 1931, when her tonsils were removed by Mr. Barrington Ward. There was an initial exacerbation immediately after the operation, which was followed by rapid improvement. Apart from a slight relapse, after a sore throat in May 1932, she has remained well.

[1] *Arch. Derm. and Syph.*, 1934, xxix, 548.

The other patient, a girl, aged 12, had had the eruption on the hands and feet for over a year when I first saw her in November 1932. She was shown at the meeting of the Section in that month.[1] The tonsils were large and infected, and there was much muco-pus in the nasopharynx. Mr. W. M. Mollison removed the tonsils, and the eruption rapidly improved. There has been no relapse.

Discussion.—The PRESIDENT said he did not think that tonsil disease would be regarded by many as causal, but it would be interesting to know what was the effect of treating the tonsils in ordinary psoriasis.

Dr. BARBER (in reply) said that in many cases of ordinary psoriasis there was apparently no association of the eruption with focal infection. The same was true of rheumatoid arthritis, which, of course, was frequently accompanied by psoriasis. In both diseases, however, there was a group of cases in which focal infection appeared to be the chief causative factor. In psoriasis there was an undoubted connexion in some cases with tonsillar infection. The eruption often came out like an exanthem after an attack of tonsillitis, whereas other acute infections often caused its temporary disappearance.

Pemphigus Vegetans, showing Result of Treatment.—H. MACCORMAC, C.B.E., M.D. (President).

E. A., who was shown at the Meeting held on December 21, 1933,[2] is now shown again to demonstrate the result of treatment.

On December 14, 1933, under a general anæsthetic, ten radium needles, each of 3 mgm., were inserted in the lower half of the tumour and removed after six days, and on January 16, 1934, the upper half was similarly treated. Following this treatment a considerable reaction developed: the tumour has gradually involuted and there are now only vestiges of the original growth. A series of four injections of germanin were given between January 11 and 27, the first dose 0·5 grm., and the remaining each 1·0 grm. This has completely stopped the development of bullæ, which up to the time of the germanin treatment were constantly present.

The results of this combined treatment have been remarkably successful and it is hoped that the patient has been permanently cured.

Discussion.—Dr. A. M. H. GRAY said that in a case of pemphigus of severe type Dr. Barber had advised treatment with antimony, and this had been continued after the patient came into hospital, but it had no particular influence on the condition. A change was then made to germanin, and for a time there was remarkable improvement, but when this drug was suspended there was a relapse. The patient was put on to germanin again, but he rapidly became worse, and died.

He had had another case, that of a woman with severe pemphigus, the eruption having commenced in the mouth. She did not appear to respond to treatment at all, and she died. Those were the only two cases which he had had the opportunity of treating recently, and both were very severe.

Had these fungating lesions ever been treated with X-rays? It seemed to him (Dr. Gray) that if they responded so well to radium, they might respond to X-rays, which would be easier to apply.

Dr. S. E. DORE said that he had treated one such case through a general practitioner with germanin. The patient had had pemphigus for a long time, and was seriously ill. A beginning was made with one-eighth, followed by one-half the ordinary dose, but each time that it was given there was suppression of urine, so that its use had to be given up.

Dr. H. W. BARBER said that the only case of true pemphigus which he had been able to treat in recent years was that of a woman who had the disease very badly—indeed he thought she would die. He tried injections of sodium antimony tartrate, which she at first tolerated well; the condition gradually cleared up in hospital, and the patient returned home. That was three years ago. He heard from her doctor that she had periodical slight relapses, and

[1] *Proceedings*, 1932, xxvi, 329 (Sect. Derm., 15); *Brit. Journ. Derm. and Syph.*, 1933, xlv, 113.
[2] *Proceedings*, xxvii, 587 (Sect. Derm. 27).

each relapse had responded to a few injections of antimony. Previously bedridden, she now performed her household duties. He had had one case since, but the patient was an aged woman, and so he did not like to risk giving antimony. He asked what was the experience of members with antimony.

The PRESIDENT (in reply) said he did not think that germanin contained antimony; he believed it to be a urea derivative.[1] He did not know whether pemphigus was now more common than formerly. One could never be sure about the effect of treatment on the disease. Some cases responded well to arsenic. A woman had come to his out-patient department with such severe pemphigus that she was taken into hospital. She was treated with high doses of Fowler's solution, and she recovered completely. That was ten years ago; he (the President) had seen her in the intervening years, and she remained well. She had severe peripheral neuritis following the treatment, but she preferred that to the pemphigus.

The present patient had had X-rays applied before the radium, and only a slight improvement had followed though a full pastille dose was given. Radium seemed to be the treatment of choice.

In the case mentioned by Dr. Barber the condition had cleared up under the treatment with quinine and hexamine, and he had successfully treated another case in the same way.

Pigmentary Eruption on Leg.—H. MACCORMAC, C.B.E., M.D.

W. B., a man, aged 67, was first seen a year ago with lichenized eczema of the wrists and an extensive patch of dry eczema on the right leg; there were also a few patches on other parts of the body.

In December last thrombosis developed in the right leg, which became swollen and painful, and this was followed by aggravation of the eczema.

The interest in the case lies in the microscopic appearances. A portion of the skin removed shows some thinning of the epithelium, with atrophy of the rete cones. There is a marked lymphocytic infiltration in the dermis and in places a large number of newly formed capillaries are seen. In a suitably stained section blood pigment can be demonstrated. This corresponds exactly with the account of the microscopic appearances in the case of Schamberg's disease described by L. B. Kingery and in the case recently shown by Dr. Klaber. The tissue reaction, it would appear, is one which may follow any form of venous stasis, as in the present case. No significance can therefore be attached to it as a distinguishing feature of Schamberg's dermatosis.

Epithelioma Adenoides Cysticum in a Woman aged 69, and in her Son aged 33.—H. CORSI, M.D.

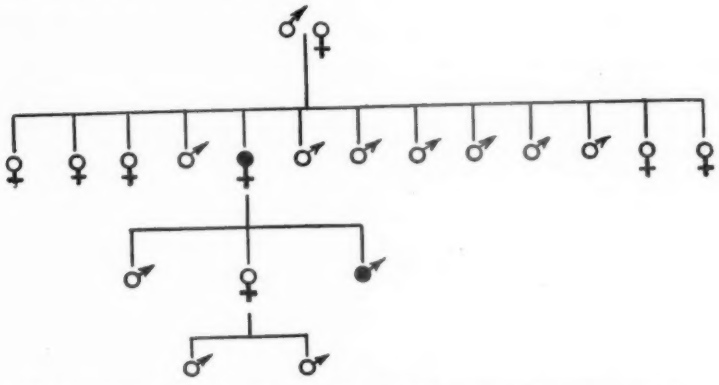
No other members of an extensive family covering three generations could be found to be affected. The condition began at the age of 14 in the mother and at the age of 19 in the son. It has been much more progressive in the son than in the mother. In the son the tumours number a hundred or more and extend in diminishing numbers right down on to the thighs. Some six or eight in the interscapular region are the size of cherries. In the mother the tumours are quite few, but two have attained the size of walnuts and have been removed.

The description originally given by Brooke or Fordyce in 1892, and several others since, exactly fits these two cases except that here the milia, which have been usually described as on or in the tumours, are absent.

The section of a tumour, the size of a cherry, removed from the nape of the neck of the mother shows the appearance of a basal-celled epithelioma with much cyst formation. In some cysts the epithelium has completely disappeared so that they consist of clear spaces in a fibrous capsule. Histologically this is not easily distinguishable from a cystic "rodent." A section from a tumour the size of a pea,

[1] Germanin is a complex organic urea compound; it is a specific for trypanosomiasis. [H. S.—*Ed. Rep.*]

removed from the son, shows a basal-celled epithelioma in which cyst formation is either absent or almost absent. Essentially, however, both sections resemble closely those shown by Brooke and others.



The two members of the fourth generation, aged 14 years and 12 years respectively, are rather too young to be affected.

Dr. J. A. DRAKE said he had now under his care an elderly woman who had a mass of tumours on the scalp, the smaller ones resembling those in Dr. Corsi's cases. Some of the tumours on the front of the scalp were growing and ulcerating. In addition there was an infiltrating condition spreading down from the scalp on to the face, suggestive of a leukæmic affection. There was a remarkable diminution in the total leucocyte count. The lesions on the head had been present for about three years. There was no family history of a similar condition.

Adenoma Sebaceum (Pringle).—ROBERT KLABER, M.D.

This boy, C. P., is aged 6. The lesions first appeared about three years ago, and have not altered very much since. They vary from the size of a pin-point to that of a pin-head. Their colour ranges from fawn to red, and they occupy the typical distribution on the central parts of the face. The forehead is clear.

The boy is said by his mother to be highly strung; this is not very evident, however, and there are no obvious signs of mental defect.

There is no family history of this or any similar condition. The mother shows well-marked hypertrichosis.

Two Cases of Schamberg's Disease.—ROBERT KLABER, M.D.

I. The patient, L. K., is a man aged 44, a bricklayer. Four months ago he noticed a patchy, red rash on the front of the left shin, and one week ago he noticed some similar lesions on the right shin. There is some superficial scaling, but the underlying lesions show a characteristic light brown pigmentation, with a few bright red spots. There is no definite venous varicosity, and no irritation at all. No family history.

The patient has recently applied iodine to the lesions, which may account for this scaliness.

II. This boy, C. W., is aged 13. Some months ago, he first noticed a few red spots on the dorsum of the left foot. Further spots then appeared further up, extending to the outer aspect of the ankle and leg. The affected area now extends along the posterior aspect of the leg and the thigh. The lesions consist of light brown macules, irregular in size and shape, with a tendency to grouping. The

lesions on the back of the thigh show a few "cayenne pepper spots," which are best observed under glass pressure. Other lesions, which are said to have been present in the knee flexure, have almost completely involuted without treatment. The lesions round the upper aspect of the ankle show a deep brownish-purple colour. On glass pressure, these lesions are observed to consist of large purpuric spots, lying on a brown background. Here the lesions show a little superficial scaling. There is only very slight and occasional irritation. There is no family history of any similar condition.

Histological Report.—Section stained with hæmatoxylin and eosin shows, lying beneath a normal epithelium, a fairly dense infiltrate, with perivascular concentrations, lying in the highly œdematous upper half of the corium. The infiltrate consists of round cells and histiocytes.

Ferrocyanide staining shows granules of iron-containing pigment, both within and outside the histiocytes.

Discussion.—Dr. KNOWSLEY SIBLEY said that he had at present, attending St. John's Hospital, an unusual case, which had been labelled one of Schamberg's disease. The patient, a healthy young man, had about twelve lesions on the left arm and forearm, but nowhere else on the body. They had been present for twelve months, and had not shown any change during that time. They had a typical cayenne pepper appearance, and Dr. Muende, who performed a biopsy, reported that the condition was, histologically, typical Schamberg's disease. Recently the man had had an attack of erythema multiforme affecting the other arm. That had disappeared within a few weeks, but the Schamberg's disease was still present.

Dr. A. M. H. GRAY said he thought that the condition in the boy was much more like angioma serpiginosum, especially because of the manner of spread down the limbs. There might be some exudate of blood pigment, but the main lesion was not a purpura; it was a distended capillary vessel which could not be emptied. His impression of cases described clinically as Schamberg's disease was that they were instances of pigmentary change unassociated with obvious hæmorrhage or any particular dilatation of the capillary vessels. A striking character of Schamberg's disease was the absence of clinical inflammation or hæmorrhage.

Dr. BARBER said he agreed with Dr. Gray that the condition in the child was angioma serpiginosum. For some years he had watched a little girl, in whom the eruption began in the pubic region. It had slowly spread upwards over the abdomen and flanks, clearing behind the spreading edge and downwards on to the thighs. Eventually it extended over the chest and shoulders to the base of the neck.

The PRESIDENT said he too agreed that the condition in the boy was angioma serpiginosum, but the opinion in some textbooks was that this was the same condition as Schamberg's disease. It was said that Schamberg's disease never occurred in women, and that the lesion was always on the leg; the distribution was where there was hypostatic congestion. In some cases it was difficult to say whether it was Schamberg's disease, or something which corresponded with varicose dermatitis. If it was Schamberg's disease it was merely a case of putting a new label on to an old disease.

Dr. KLABER (in reply) said that he had brought up these cases as the subject was so obscure that he thought it would be of value to provoke a discussion on Schamberg's disease. He fully associated himself with the President's remarks on the subject.

In common with the sections from the four cases which he (Dr. Klaber) had regarded as examples of Schamberg's disease, the sections in the President's case of hypostatic eczema showed œdema of the corium with a lymphocytic infiltrate and a deposit of iron-containing pigment. But, the President's sections, as might be expected, showed well-marked œdema of the prickle-cell layer—the status eczematus. No such epithelial change was present in any of the sections which he (the speaker) had shown from the four cases of Schamberg's disease.

Angioma serpiginosum appeared to be a more popular diagnosis than Schamberg's disease in the case of the boy. He (Dr. Klaber) was not clear as to the possible closeness of relationship between these two conditions.

He had understood, however, that while epithelial changes were absent in Schamberg's disease they were always present in angioma serpiginosum.

Parapsoriasis en Plaques.—HUGH GORDON, M.C., M.R.C.P.

Patient, female, aged 18, when first seen two years ago had had the eruption for two years. It was definitely suggestive of pityriasis rosea, though the history made this diagnosis improbable. There were, however, a few medallions with typical pityriasis scaling on the front of the chest. In other places the eruption was composed of flat papules and macules on the trunk, extending down the arms to the elbows and legs to the knees. The macules were confluent on the scapular regions with bran-like desquamation.

General carbon-arc baths were ordered and continued for three months with no result. Local treatment, which was varied, was also useless. The comparative effect of X-rays and Grenz rays was tried a year ago, the right side of the body being given two exposures of X-ray ½B and the left side three applications of Grenz rays, each 300 *r*. The X-rays made no difference, but the left side cleared up to some degree, with pigmentation, as a result of the Grenz rays, but has since relapsed.

The areas involved have spread gradually within the last two years, and the lesions have become confluent in places.

[*The report of other cases shown at this meeting will be published in the next issue of the* PROCEEDINGS *of the Section.*]

Section of Medicine

President—Sir FARQUHAR BUZZARD, Bart., K.C.V.O., M.D.

[*March* 27, 1934]

RECENT ADVANCES IN THE PATHOLOGY AND TREATMENT OF LYMPHADENOMA

Dr. M. H. Gordon: Lymphadenoma occupies a position in the marches of medicine forming a link between the granulomata of known ætiology and malignant disease. For that reason the problem of its ætiology may well be a key position, as conceivably the knowledge thus obtained may pave the way for a successful attempt on sarcoma, the form of malignant disease nearest to it.

Lymphadenoma has been described as a specific disease affecting primarily the lymphatic glands and spreading thence to other organs. In a typical case the histological changes are so characteristic that the diagnosis can be made with reasonable certainty from the section of an enlarged gland. When the three characteristic changes of fibrosis, giant cells, and eosinophils are all present, the evidence for lymphadenoma is complete. In practice, however, a considerable number of cases occur in which one or more of these three changes are lacking. There may be proliferation of the reticulo-endothelium without typical giant cells, or the fibrosis and eosinophils may be lacking. In such atypical cases the histological diagnosis is on far less secure ground.

From what I have seen of them I suspect that there are a number of distinct conditions hitherto undifferentiated in this group of atypical cases. There seem to be a series of gradations between typical lymphadenoma and typical lymphosarcoma or reticulosarcoma. The term "Hodgkin group" has come into use for these conditions and seems to be a convenient one until we know more.

Looking at the present position broadly, it is clear that hitherto we have been limited to clinical methods and to anatomical pathology (macroscopic and microscopic) for such incomplete knowledge as we have of lymphadenoma. On the other hand, we have a definite disease, with specific clinical and histological features that should enable it to be recognized if reproduced in an animal. The course of the disease is suggestive of an infective agent, but its apparently uniform fatality tends to bring it closer to malignant disease than to the granulomata.

Experimental studies.—Lymphadenoma, so far, has not been identified in animals, nor has it been communicated to them with certainty. The ætiology therefore is an extremely difficult problem to attack experimentally, and it is improbable that the solution will be arrived at without casualties among investigators. That, however, makes it all the more attractive.

A priori it seems possible that when the pathogenic agent does come to light it will be found to be more nearly allied to that of sarcoma than to the granuloma-producing agents at present known. From her careful study of the histology Dr. B. D. Pullinger considered it to be most closely allied to leukæmia. It is possible, however, that in ætiology leukæmia is closely allied to sarcoma.

During the past six years, with the cordial co-operation of the staff of St. Bartholomew's Hospital, an attempt has been made to obtain further light on the ætiology of lymphadenoma. So far, the investigation has proceeded along three lines. (1) Search for a pathogenic factor in glands removed from lymphadenoma cases. (2) Microscopical studies of this material for the presence of an organized agent. (3) Allergic tests. So far as possible, procedure has been from the known

to the unknown, and the results have been checked by the examination of control glands from other diseases. In the first place known granuloma-producing organisms were looked for. With efficient asepsis, cultures made on ordinary media with various enrichments remained sterile. Spirochætes were next searched for, employing material known to contain spirochætes to control the methods. Pseudospirochætes were encountered especially in some preparations of lymphadenoma tissues intensely stained by silver, but no evidence of spirochætal infection could be obtained. Tuberculosis was next searched for by direct injection of guinea-pigs with a standardized procedure, the animals being kept for as long as possible. The results are summarized in the following table :—

TABLE I.—CAPACITY OF GLANDS TO PRODUCE TUBERCULOSIS IN THE GUINEA-PIG.

Condition	Cases	Positive	Negative
Lymphadenoma	40	3	37
Control Glands			
Carcinoma	8	1	7
Sarcoma	8	1	7
Indeterminate	19	0	19
Total controls	35	2	33
Tuberculous glands			
Endothelial T.	5	1	4
Caseating T.	10	10	0

No evidence was found therefore that the tubercle bacillus of human or bovine type plays any important part in lymphadenoma.

Avian tuberculosis.—The suggestion of L'Esperance that lymphadenoma may be due to the avian form of the tubercle bacillus was investigated by injecting glands from six cases of lymphadenoma into mice. The result was negative. Dr. Garrod injected pigeons from a particularly active and typical case, without effect. Van Rooyen, also in a careful piece of work, has excluded avian tubercle as a factor in lymphadenoma. Search was next made for evidence of the presence of mycotic infection, but here again the results were negative. Organisms known to be capable of producing granuloma having thus been excluded in turn, search was next made for evidence as to the presence of a virus infection. Twort had previously shown that on subcutaneous injection into guinea-pigs, lymphadenoma gland suspensions may give rise to a local inflammatory nodule in which no micro-organisms can be found. This was confirmed, and the observation made that in some acute cases the reaction of the subcutaneous tissues of the guinea-pig may be pronounced. With gland suspension from an early case, where the disease was particularly acute, serial passage of this local subcutaneous granuloma was obtained through four guinea-pigs in succession, the material being sterile throughout, but, so far, I have not been able to confirm that single observation. In my experience, suspensions of control glands when sterile do not produce this result, but unfortunately it does not always occur with glands from undoubted cases of lymphadenoma.

Cerebral route of inoculation.—My early attempts to produce any effect on laboratory animals by injecting them cerebrally with suspensions of lymphadenoma glands were unsuccessful: probably the material was not suitable, or the dose insufficient. In the autumn of 1930, however, Hellerstrom and Wassen of Stockholm reported that they had succeeded in producing meningo-encephalitis in monkeys by cerebral inoculation of pus from the glands of cases of lymphogranuloma inguinale, a benign condition that appears to belong to the lymphadenoma group because glands are specially involved, and there is a reaction of the reticulo-endothelium before necrosis and suppuration of the affected glands. This successful experiment of the Stockholm observers was soon confirmed and serial passage obtained. The agent was thus shown to be a virus and is now established as

the cause of lymphogranuloma inguinale. Accordingly, when suitable material from lymphadenoma came to hand, the cerebral inoculation of animals was resumed, using a more efficient technique—employing broth for the suspensions of the gland and allowing these to autolyse for some time in the refrigerator before injection. As a result of this improved technique an encephalitic condition frequently fatal was found to be produced both in the rabbit and guinea-pig, though not so far in the mouse or monkey. After an incubation period of one to several days these animals may develop symptoms similar to those produced by well-known viruses (vaccinia, herpes, psittacosis), such as fits, salivation, head turning, tremors and pareses, but the characteristic condition produced by lymphadenoma glands is one of inco-ordination and ataxia accompanied by rigidity of the muscles and a spastic gait. In severe cases also opisthotonus is occasionally produced.

The first step was to see whether this curious action of lymphadenoma glands on the rabbit's brain can be applied for diagnosis. This matter has been under investigation now for over three years, during which time glands of all sorts, but chiefly those removed for biopsy when, on clinical grounds, lymphadenoma seemed possible, have been submitted to the rabbit test with the following results.

TABLE II.—BIOLOGICAL TEST (RABBIT). RESULTS GIVEN BY GLANDS FROM LYMPHADENOMA AND OTHER CONDITIONS. (FEBRUARY 1931 TO MARCH 1934.)

Condition	Cases	Positive	Negative
Lymphadenoma	35	30	5
Non-lymphadenoma Cases			
Hyperplasia only	14	0	14
Adenitis	11	0	11
Tubercle	14	0	14
Carcinoma	6	0	6
Sarcoma	12	0	12
Leukæmia	5	0	5
Various: normal, allergic, etc. ...	5	0	5
Total ...	102	30	72

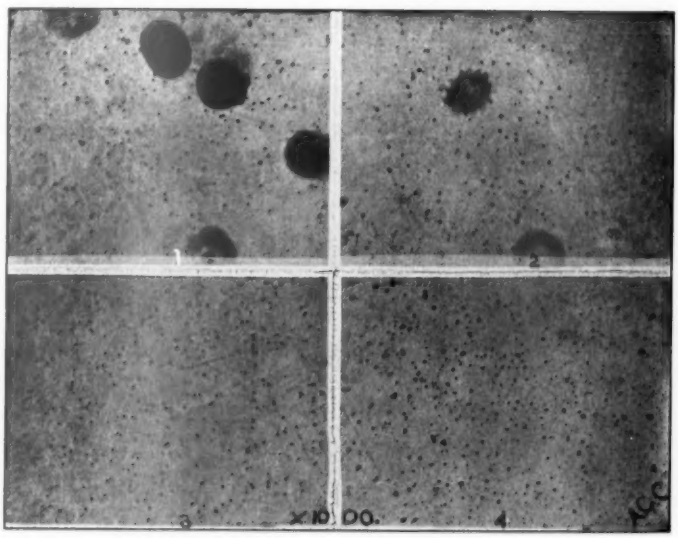
From the figures recorded in the table it is plain that since glands from other conditions give negative results, this biological test is capable of performing useful service in the practical diagnosis of lymphadenoma. So far, I can only recall three cases in which a mistake was made and in all of them the error was one of interpretation, a weak positive with the raw material alone being regarded as positive. In typical cases the reaction is pronounced both with the raw material and with the same after it has been heated for thirty minutes to 65° C.—a point especially useful when dealing with contaminated material. The value of the test for diagnosis has been confirmed by van Rooyen (Edinburgh) who has obtained positive results in 15 out of 20 cases of lymphadenoma and negative results with glands from other conditions. Moreover, both at Edinburgh and in London, glands from certain cases in the post-mortem room, where the naked-eye lesions indicated a new growth in the lung, have been correctly diagnosed by this biological test on the rabbit and this result confirmed by the subsequent histological examination. The test seems to be of chief value in early cases of lymphadenoma; later when the disease has become chronic, the glands not infrequently give negative results. The strongest reaction seems to occur when all the three cardinal histological changes previously mentioned are present in the glands.

The nature of the pathogenic agent present in the glands and concerned in this biological reaction is not yet settled. It resists exposure for thirty minutes to 65° C., but is inactivated in that time at 80° C., and this pronounced thermostability distinguishes it from most of the known viruses, though not from all. Its presence in a given suspension increases as time goes on—apparently from autolysis of the cells—and in glands from acute cases it can then be detected sometimes up to

a dilution of 1 : 200. With such material I have confirmed van Rooyen's observation that it is filtrable through bacterial filters such as the Seitz. The agent withstands antiseptics such as carbolic well, but is gradually attenuated by ether. Van Rooyen finds that the reaction of the suspending fluid is important and that X-rays in moderate doses do not inactivate it. So far, successful passage has not been obtained, in spite of many attempts. Although neither is at all easy to demonstrate, I have obtained evidence that some degree of both active and passive immunity can be obtained.

By the cerebral inoculation of rabbits, Friedemann has found that in normal rib-marrow, and sometimes in the spleen, an agent is present which produces symptoms resembling those evoked by suspensions of lymphadenoma glands. Recently he has brought forward further evidence in favour of this being a proteolytic enzyme and evidently thinks that the two agents in marrow and lymphadenoma gland are the same. Now it so happens that for some years past I have been comparing the proteolytic activity of suspensions in broth of various tissues (obtained chiefly post mortem) by measuring their capacity to affect carbolized litmus milk in twenty-four hours at 55° C. In these observations a duplicate has usually been carried out with the same material after it had been heated for thirty minutes to 65° C. In this way it came to notice that bone-marrow (especially rib-marrow) is perhaps the most strongly proteolytic tissue in the whole body, producing usually well-marked precipitation and digestion of the milk up to a dilution in broth of 1 : 10,000 or 1 : 20,000. Spleen pulp is also active in lactolytic effect, commonly going to 1 : 1,000. On the other hand, lymphadenoma glands are usually negative in this test at the first dilution to be tested, namely 1 : 20. It seems to me unlikely, therefore, that the pathogenic agent in these glands can be a proteolytic enzyme. At the same time, passage has not yet been obtained and it may be that this active agent in lymphadenoma glands is complex, and in part derived from the cells. In common with van Rooyen, however, I have been unable, so far, to associate the presence of the agent with any particular cell reaction in the lymphadenoma glands.

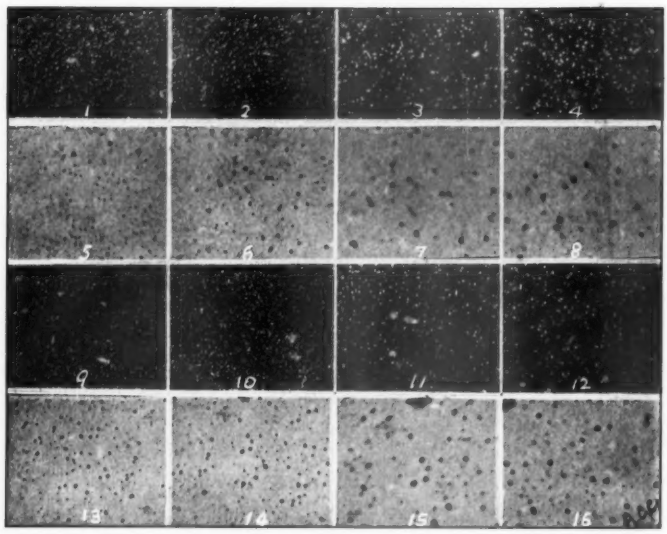
In view of Professor Friedemann's interesting observations I have recently examined specimens of marrow and found that fœtal ribs and spleen contain neither a proteolytic, nor an encephalitogenic agent. A child's ribs at term were equally negative. By the thirty-third day, however, both were present in the rib-marrow, and eight out of ten adult rib-marrows were also positive in both respects. Pus gives almost—if not quite—as high a proteolytic titre in the milk test as marrow, and all of eight specimens tested gave high readings, yet when injected into the rabbit's brain six of them were negative. Of the two positive specimens, one came from a case of pneumococcal empyema following appendicitis, and the other from a case of staphylococcal osteomyelitis. Although in some of the rabbits inoculated cerebrally with marrow the symptoms closely resemble those produced by lymphadenoma glands, it has seemed to me that in most of them the chief effect is one of paralysis, far more so than is usually the case with lymphadenoma glands suspensions, and I am not satiefied that the conditions induced are identical. Friedemann failed to find his encephalitogenic agent in the marrow of animals such as the dog and horse. Through the kindness of Colonel Hamerton I have recently been able to test rib-marrow from a bear and a leopard ; both gave good proteolytic readings, bear to 1 : 5,000, leopard 1 : 10,000, but neither of them contained an encephalitogenic agent for the rabbit. The problem of the relation of these two agents therefore is complex and requires further investigation. The manner in which they act is also at present obscure. Whatever the outcome may be, the presence in marrow and pus of an encephalitogenic agent does not invalidate the diagnostic value of the rabbit test when applied to glands from suspected cases of lymphadenoma. This is now an established fact.



Photomicrographs taken by Alfred C. Coles, M.D.

I.—Hodgkin bodies. × 1,000. *Stain : Giemsa.*

Figs. 1 and 2 from retroperitoneal gland.
Fig. 3 from aspirated gland fluid during life.
Fig. 4, Paschen bodies from vaccinia (child).



Photomicrographs taken by Alfred C. Coles, M.D.

II.—Figs. 1 to 8, Hodgkin bodies from lymphadenoma. Figs. 9 to 16, Paschen bodies from vaccinia (child).

Figs. 1, 2, 9, 10 taken with $\frac{2}{3}$ in. or 16 mm. objective, + comp. oc. 8 × 160.
Figs. 3, 4, 11, 12 ,, ,, $\frac{1}{3}$ in. or 8 mm. ,, ,, ,, ,, × 400.
All on dark ground.
Figs. 5, 6, 13, 14 taken with 2 mm. objective and oc. 3 × 1,000.
Figs. 7, 8, 15, 16 ,, ,, ,, ,, comp. oc. 8 × 1,500.
All Giemsa stained, taken on two $\frac{1}{4}$ plates at precise magnification stated.

Elementary bodies.—Recent work on vaccinia has proved that the well-known elementary bodies of Paschen are the actual virus of that disease. It was of much interest therefore to find that bodies closely resembling these vaccinia bodies are present in large numbers in suspensions of lymphadenoma glands. The presence of these bodies in lymphadenoma has been confirmed by Dr. A. C. Coles who has generously permitted me to show his most instructive photographs, both of them and of Paschen bodies, in the accompanying plate.

Allergic tests.—Throughout the present inquiry Dr. James Maxwell has tested the cutaneous allergy of lymphadenoma cases. The results with tuberculin and with extracts of fungi were negative. A boiled extract kindly prepared by Dr. Wilson Smith by his own method from dried lymphadenoma glands has recently been tried. The results will be referred to by Dr. Gow.

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Dr. A. E. Gow: The last occasion when the subject of lymphadenoma was considered by the Society was in January 1926, when the Section of Medicine held a joint discussion with the Section of Comparative Medicine on "Hodgkin's disease in Man and Animals" [1]. Sir Humphry Rolleston opened that discussion on behalf of the Section of Medicine, and with regard to terminology I have nothing to add to what he said on that occasion, but the last few years have shown us that the term lymphadenoma denotes not a single disease, but several morbid processes, which, though much alike in their general clinical characteristics, yet show minor differences in their symptomatology, course, prognosis and therapeutic response. This, of itself, is of interest in that Hodgkin's original paper, contributed by Dr. R. Lee [2] in 1832, concerns a *group* of diseases as witness the differentiation of leukæmia, sarcoma and tuberculosis since. In 1926 Sir Humphry said that "as the cause of Hodgkin's lymphogranuloma is unknown, it is necessary to fall back on its histological structure as the only means of defining exactly what is meant by the name. The histological appearances described independently and almost simultaneously by Andrewes [3] in 1901 and Dorothy Reed still hold good." But the giant-cell of lymphadenoma was known long before this. In "Lectures on Pathological Anatomy" by Wilks and Moxon (second edition 1875), in the description of lymphadenoma it is written "The very soft forms, too, have often large polynucleated cells." This may be in the first edition also, but that I have not seen. It is unnecessary therefore to associate these characteristic giant-cells with the names of individual pathologists who investigated the disease over twenty years later.

These histological changes concern the reticulo-endothelial cells in lymphoid tissue. The endothelial cells line the spaces, while the reticulum cells form a cover for the fibrous network and develop either fibrous tissue or stem cells which again give rise to eosinophil cells and perhaps to polymorphonuclear leucocytes. In lymphadenoma both endothelial and reticulum cells show overgrowth, either severally or together; mononuclear elements fill the gland, obscuring the normal structure. Endothelial cells give rise to giant cells, the presence of which is generally considered essential for the histological diagnosis of Hodgkin's disease. In some cases mononuclear cells proliferate throughout the gland, there is no

fibrosis and few giant cells. Here is an example of this reticulosis (figs. 1 and 2)—the gland was removed from the right supraclavicular fossa of a boy, aged 17, who had, for the past 2½ years, noticed lumps in the neck, which varied in size. A year ago he had bronchopneumonia, and since then a "bunch of grapes," to use his own expression, has existed across the root of the right neck—about ten ovoid, firm,

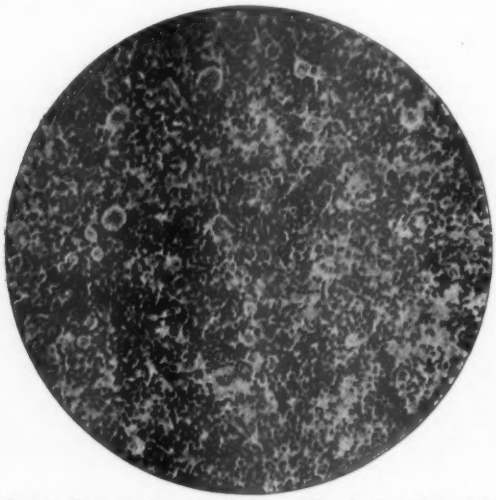

FIG. 1.—Mononuclear reticulosis: no fibrosis: few giant cells.

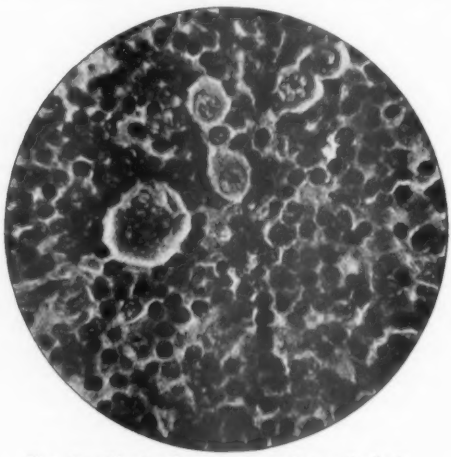

FIG. 2.—Giant cells in mononuclear reticulosis.

smooth, painless, insensitive, discrete nodes, and he shows the filling of the infraclavicular fossa, due to involvement of glands on the costo-coracoid membrane—a sign of value in the differential diagnosis of the Hodgkin group from some other causes of enlargement of lymph nodes in this area. Two glands are just palpable in the posterior triangle of the neck on the left side. Apart from some sweating there are no other symptoms or signs; the boy has gained 7 lb. during the past year.

There is no pyrexia, no pruritus, no evidence of visceral infiltration. The blood picture is well within the limits of health. The biological test in rabbit brain is negative for Hodgkin's disease. Treatment was by X-rays, fourteen doses distributed over the neck, mediastinum, and groins, 180 kilovoltage; current 8 ma. Focus skin

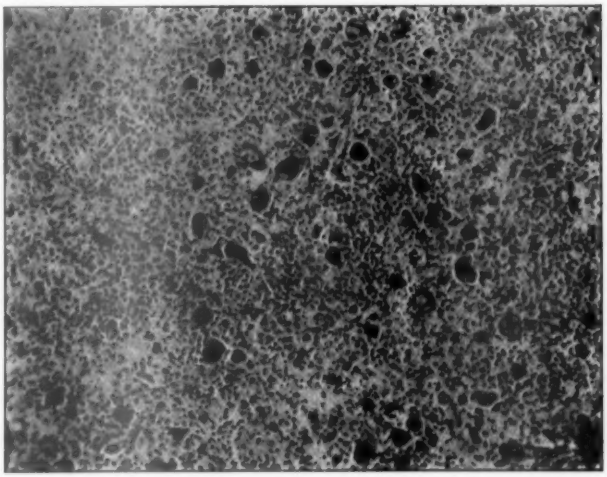

FIG. 3.—Section of lymph node showing giant cell tumour of reticulum.

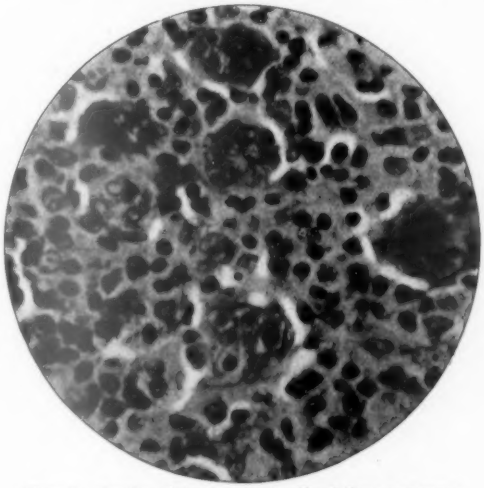

FIG. 4.—Section showing giant cells of the same case.

distance 40-45 cm., filter 0·5 mm., unit skin dosage at each sitting 30-35%. The glands are no longer palpable and I believe the prognosis in this type of case is good.

A man, aged 31, was believed, on clinical and histological grounds, to have acute lymphadenoma. Actually he had a giant-cell tumour of the recticulum (figs. 3 and 4).

The biological test was negative. Dr. Robb Smith is investigating this particular group from the histological point of view. The illness, which lasted nine months, began with weakness and enlargement of the liver and spleen; glandular swellings soon appeared in the neck, axillæ, and groins, and pyrexia of the Pel-Ebstein type developed. The blood picture was that of a high-grade anæmia with leucopenia (figs. 3 and 4, p. 55).

Intradermal allergic test.—Wilson-Smith has demonstrated that a boiled extract of vaccinia virus prepared by his method is efficacious, when injected intradermally, for demonstrating specific allergy in persons who have had vaccinia—a known virus disease. Lymphadenoma may be a virus disease, and the experiment has been repeated, using as antigen a boiled extract of dried lymphadenoma gland, prepared by Wilson-Smith. No reaction was obtained with the first antigen prepared from raw lymphadenoma gland. The gland dried in vacuo was next extracted in the same way, and has been tested by Dr. Maxwell on about thirty patients, of whom ten were controls and all were negative, The great majority of patients known to be suffering from Hodgkin's disease have also proved negative, but in three instances where the disease appeared to be "resting," a small local reaction, varying from a few mm. to a cm. in diameter, appeared within twelve hours. The best reaction of all, however, measuring 3 cm. in diameter, occurred in the case of a woman (G. P.) aged 34, whose glands showed histologically definite evidence of lymphadenoma, but gave a negative biological test. This patient had been ill for more than three years; she suffered much from pruritus and the glandular swellings were usually painful at their onset and tender on palpation. In this respect the intradermal test appears to be generally similar to the von Pirquet reaction.

Specific therapy.—The possibility that lymphadenoma is a virus infection is beginning to receive considerable laboratory support, but clinically the disease bears no resemblance to other known virus conditions in man other than lymphogranuloma inguinale (Oriental bubo)—a venereal disease. The general appearance of broken-down glands in lymphadenoma corresponds closely with that described in lymphogranuloma inguinale by Sabrazés [4] in his monograph on lymphadenoma and this disease. Psittacosis also has some points of resemblance. Various attempts at specific treatment have been made—so far unsuccessfully. A woman (D. D.) aged 28, developed severe pruritus while pregnant; this symptom persisted until she died, emaciated and in coma, three years and eight months later. During the course of the disease all superficial groups of nodes were involved, many of which were tender; a mass developed in the right renal region. An unusual happening in my experience was the development of multiple ulcers on the tongue and cheek; this also occurred in the next case to which reference will be made. I do not know of any observations on the gastric juice in lymphadenoma; it would be interesting if hypochlorhydria were found, especially as some cases terminate with the clinical picture of aplastic anæmia. For the last three months of her illness this patient was paraplegic, without X-ray evidence of vertebral infiltration. The patient was treated by irradiation, arsenic by three routes and iron. Nothing was found to control the pruritus. Histological and biological tests were positive for Hodgkin's disease.

The first attempt at specific therapy was with prepared chicken serum, according to the method of Utz and Keatinge [5]. One injection of the gland suspension is given subcutaneously to the bird; blood is withdrawn from seven to ten days later and the serum used without heating. Others have tried this form of treatment. Barrett and Bond [6] treated four cases of lymphadenoma at St. Thomas' Hospital with chicken serum prepared according to the Utz and Keatinge method; two of the patients were at an advanced state when the treatment was begun but in the two others their condition was more favourable. The conclusion was reached that the treatment was of no avail. Dr. Pulvertaft [7], at the Westminster Hospital, treated, with a modified

method, five cases; though the patients felt better after the injection the effect on the progress of the disease was disappointing. McGrath [8] has reported four cases so treated without benefit.

Later a suspension of the patient's own gland, attenuated by 10% ether, was administered intramuscularly. This extract appeared to ease pruritus for twenty-four hours but it was followed by appreciable swelling of the nodes in the neck and face, some of which ultimately broke down; it is therefore justifiable to assume that the extract contained some active agent.

M. B., a woman, aged 30, has been under observation, on-and-off, for three and a half years. Her illness began with the development of a hard painless swelling at the root of the neck on the right side. Subsequently most of the superficial nodes became enlarged and masses developed in the mediastinum and in the abdomen. A gland examined histologically showed the typical Hodgkin lesions (fig. 5), and also

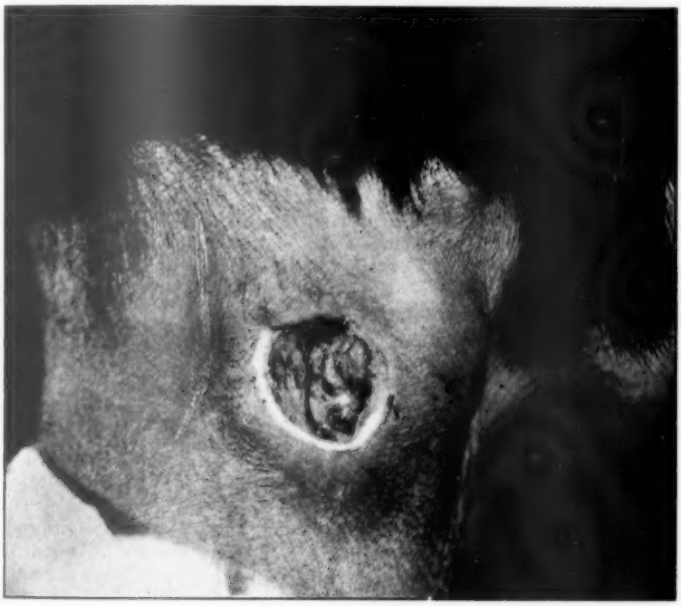

FIG. 5.—Photograph of broken-down gland in neck, showing undermined shelving border and ragged, indolent base of the ulcer.

proved positive to the biological test. Tonsillitis was followed by swollen glands in the left neck which never subsided and erysipelas of the left arm shortly preceded the development of a painful swelling in the left axilla; this gland varies in size and in tenderness. A sequel to a second attack of erysipelas, involving the chest and left arm, was the breaking down of glands in the right side of the neck and later in the axilla with the formation of very large fungating granulations; on the first occasion pus aspirated was sterile but later hæmolytic streptococci and staphylococci were isolated. The patient had two courses of sensitized vaccine, prepared by Dr. Gordon.

For this vaccine the gland is ground up by hand in a mortar in saline or broth to make a 1 : 10 suspension; 0·5% phenol is added as a preservative. 0·1 c.c. of the

1 : 10 suspension is diluted to 5 c.c. with saline and 5 c.c. of recently prepared rabbit serum ; 4-5 intravenous injections of the gland suspension in increasing doses at weekly intervals. The serum then flocculates the gland suspension. It is left in contact overnight, and then centrifuged ; and the supernatant fluid is poured off, the deposit is washed and put up in phenol saline. The first dose corresponds to 1 : 50,000 of the gland.

The first dose of 1·5 c.c. of the 1 : 50,000 was followed in half an hour by a sensation of tingling in the glands of the neck and a mild febrile reaction ; two injections on following days caused no obvious local or general disturbance. Three doses of 1 : 20,000 were followed by marked local and general reaction, the evening temperature rising to 101°. Three days later the fungating gland in the right neck was much smaller and the discharge from the axilla considerably decreased (fig. 5, p. 57). The spread of the disease is, however, not arrested, as the patient has developed in the interarytenoid region an ulceration which Mr. Bedford Russell likens to that sometimes seen in tuberculous laryngitis, and a mass has appeared in the substance of the left biceps, not attached to the humerus ; this is insensitive, but is painful after handling.

L. G., female, presents many features of interest both from a clinical and from a pathological point of view. Her father, whom I did not know, is reputed to have died from lymphadenoma five years before the onset of the patient's illness ; her mother contracted the disease in an acute form nearly four years after the daughter became affected, and died within eleven months. Two members of the same family, who contracted lymphadenoma simultaneously, have been reported recently by McHeffey and Peterson [9] in America. Another point of interest is that three months before the first enlargement of glands was noted—again above the right clavicle—this girl, aged 18, had "eczema" of the neck—an actual sore in the mid-line, which was open for 7 or 8 weeks—a possible portal of entry of infection—though the skin in this area was frequently rough and scaly for short periods during the first three years of her illness. She also developed papules on the fingers which persisted for some six months, each consisting of a hard infiltration of the skin about the size of a lentil, the older ones being paler and umbilicated. By the time of the glandular enlargement, pruritus was present when dressing in the morning and sweating was another feature. In the early stages the glands varied in size and were larger when the patient was tired or worried. In a period of apparent quiescence, after a course of irradiation, she was thrown badly in the hunting field ; within thirty-six hours the glands had swollen up again, showing, I believe, that the causal agent was still active. The course of the disease was by exacerbation and remission for three years ; then the mediastinum and mesentery were involved, leading to bilateral hydrothorax, ascites and obstructive jaundice. Pyrexia only developed during the last five months, when wasting was extreme, and death took place four years and eight months after swelling of the gland was first noticed. It was remarkable how the patient's spirits and appetite kept up almost to the end.

M. F., male, aged 19. The gland in this case shows the histological changes of Hodgkin's disease. There is little fibrosis, but there is intense eosinophilia and active proliferation of reticulum cells (fig. 6). The patient's blood showed no eosinophilia. Since the age of three he had had recurrent swellings in both sides of the neck, visible and palpable, varying in size, never very large, and quite painless. They used to last for about a fortnight at a time, at intervals varying from two months to a year. At the age of 19 the swelling was more marked on the right side than on the left and extended lower down than before. It was at this stage that the gland was removed (fig. 6). The patient died a year later and Professor A. J. Hall reports that, though the spleen was never palpable, during the last two months the mediastinal glands enlarged greatly and a pleural effusion developed. The mesenteric glands enlarged, with ascites and jaundice. The patient became pyrexial and extremely

anæmic, and he wasted profoundly. He had several injections of serum obtained from a goat to which Dr. Gye, at Mill Hill Laboratory, had given many injections of lymphadenoma-gland emulsion; but this was late in the course of the disease, and, except that for a few days after the injections the temperature fell somewhat, the administration of the serum did not produce any obvious change.

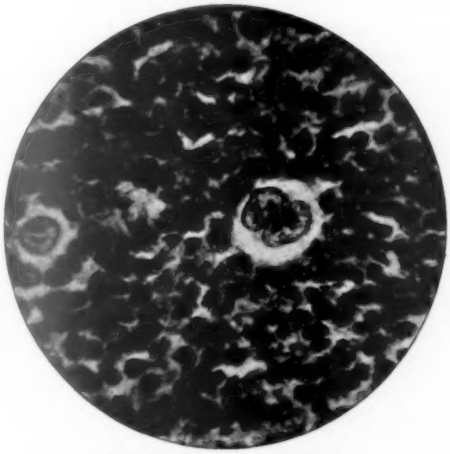

FIG. 6.—M. F. giant cells.

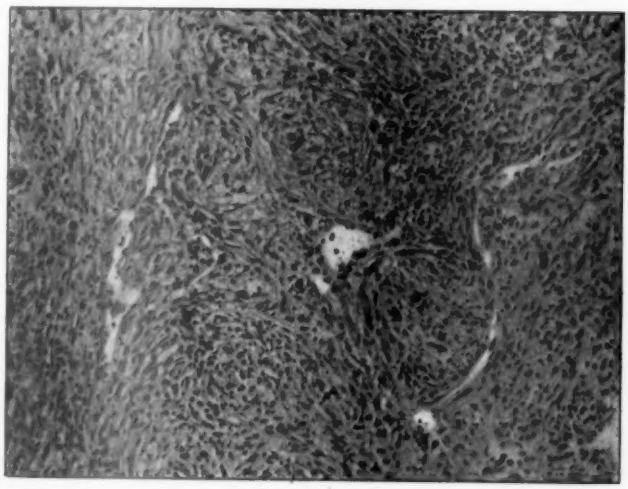

FIG. 7.—Section of gland showing fine fibrosis. The resemblance to sarcoma is, in parts, very close. Total duration of illness, 14 months.

O. R., male, age 11. Total duration of disease, fourteen months. The gland is of the fibrous type and gave a positive biological reaction. The resemblance to sarcoma is in parts very close, and this may well be an example of a link between lymphadenoma and sarcoma (fig. 7). The patient had enlarged glands in the

mediastinum, abdomen and neck. From the pleural cavity a turbid yellow fluid was aspirated; on standing a firm clot formed. The cellular content was: polys. 2%; lymphos. 96%; basos. 2%. No eosinos. X-ray examination of the femora, undertaken on account of recurrent attacks of pain in the region of the trochanters, shows some expansion of the bone, diminishing as it goes downwards to the middle of the shaft. The cancellous tissue is rarefied, giving an appearance of cavities with well-marked trabeculæ surrounding them. The compact tissue appears to be absorbed in places, and there is a large amount of periosteal new bone formation.

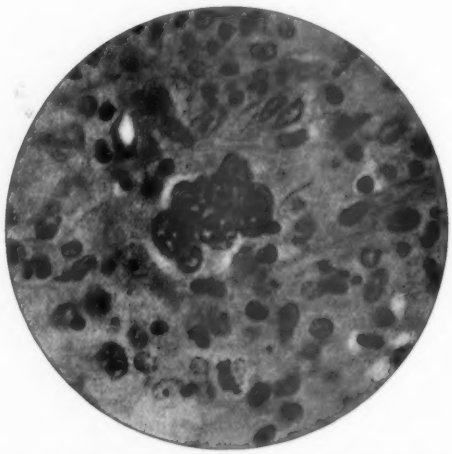

FIG. 8.—Giant cell and eosinophil cells with fine fibrosis.

V. B., male, aged 26. An acute case, duration seven months. Onset with weakness. Typical Pel-Ebstein temperature. The gland shows a moderate degree of fine fibrosis (fig. 8)—a condition often found in the acute form of the disease.

With regard to the effects of modern treatment—that is, mainly, irradiation—on the duration of the disease there can be no doubt that life is prolonged. Of thirty cases diagnosed as lymphadenoma which I analysed in 1910, the average duration was twenty months, the shortest being six and a half weeks and the longest—a very doubtful case—seven years. But what is perhaps more important, the periods of remission, particularly in the earlier stages of the disease, are prolonged, and patients are able to resume their occupation seemingly well.

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Dr. W. M. Levitt (communicated): We have now reached the position that when presented with a localized focus of lymphadenoma we can practically promise its disappearance with adequate X-ray treatment. The same statement applies to multiple localized foci of the disease, and, in fact, the extent to which this process can be carried out is only limited by the fact that there is a limit to the total amount of X-ray energy which can be poured into the body without producing fatal or even serious effects. It is important to realize that the disappearance of lymphadenomatous masses induced by X-rays is not only clinical, but also histological. In spite of the local success, we know that lymphadenoma cannot be cured by X-rays, except perhaps in rare instances. We know that recurrences appear either in the initial site or in other glandular areas, and that although these recurrent lesions also respond to X-ray treatment, sooner or later the disease so becomes widely disseminated in the chest and abdomen that we cannot apply the dosage necessary to secure regression of all the lesions. That even at this stage the disease is still radiosensitive we know from the fact that treatment is frequently successfully undertaken for the relief of pain and other pressure symptoms due to local masses. Until late in the disease, the characteristic cachexia improves *pari passu* with the disappearance of the local masses. When, however, the disease becomes too extensive for further treatment, the cachexia becomes a dominant feature.

After the initial treatment, the time that may elapse before recurrence varies greatly. Only too often it is a matter of a few months, but occasionally the patient may remain in apparently good health for one or two years or even longer. The interval tends to become shorter with successive recurrences, and in the end-stages the disease becomes more resistant to the rays, so that larger doses are required to secure regression of the masses. The total duration of the disease varies correspondingly. It is usually a few years after coming under observation, but occasionally life may be prolonged for ten years or even longer. On the other hand, in the cases in which the disease is generalized, and especially when the deep glands are already affected on coming under observation, the duration may be measured by weeks rather than months.

Such, then, is the present position with regard to the X-ray treatment of lymphadenoma—almost magical in its results in the earlier stages, frequently useless and indeed, if injudiciously used, worse than useless in the end stages. The failure to maintain a result obtained in the early stages of lymphadenoma is one of the most disappointing things with which we have to deal, and we have to inquire why it should be so.

I think that possibly, when our attention is first called to a lymphadenomatous mass in a given region without evidence of disease elsewhere, we have been too ready to assume that the palpable mass must be the initial focus of the disease. Yet we often find that though the initial focus, once treated, remains without recurrence, perhaps until the end of the patient's life, deposits in other regions follow in quick succession. Can it be that the initial lesion is, in the majority of cases, in some of the deeper glands, and the first discoverable lesion is a secondary deposit? We know for example that certain other diseases affecting lymphoid tissue, such as lymphosarcoma, have their favourite sites of origin. May it not be that the same applies to lymphadenoma? Suppose that it could be shown that in a substantial percentage of cases the disease began in, say, a certain group of abdominal glands, there would at least be a ray of hope that if this group of glands were adequately irradiated in every case a permanent result might be obtained in at least a small proportion. Moreover, arguing on these lines, one could explain the rare instances in which cure has been claimed for X-ray treatment in lymphadenoma, on the grounds that these cases were the exceptional ones in which the earliest observed lesion was the actual initial focus of the disease.

The possibility of lymphadenoma having an origin which, because of its position, escapes X-ray treatment in most cases until it is too late, has therefore to be considered. Such a primary growth would act as a reservoir of disease in the body, and might explain why the end-results of X-ray therapy in lymphadenoma are even worse than in certain varieties of malignant disease.

For the answers to these questions we must look to the pathologist, and it will be seen that from the point of view of the information required the disease requires study from a somewhat different angle. While the pathologist has hitherto tended to focus his attention on questions relating to the *genesis* of lymphadenoma, it is upon problems of the *distribution and march* of the disease that radiotherapists most require information.

In the absence of definite information upon these points, the question of what regions should be irradiated in lymphadenoma, apart from those obviously affected, is difficult. For many years it has been taught by Finzi that the mediastinum should be treated in every case of cervical gland lymphadenoma, and this is the practice at St. Bartholomew's Hospital. It is, however, when we come to consider whether the abdomen should also be included in the irradiation that we meet with most difficulty, because, while the mediastinum and several glandular areas can be dealt with without producing any severe effect upon the patient's general condition, this cannot be said of the abdomen. The effects of X-ray treatment on the abdomen, especially when such treatment is also being applied to other regions, are quite severe, and would result in the incapacitation of the patient for many weeks. Such treatment, therefore, is not undertaken except in the presence of a real indication, and it has so far not been the practice to apply X-rays to the abdomen as a routine treatment of all cases of lymphadenoma. Whether or not a case exists for the application of the treatment to the abdomen, either as a routine method in all cases of lymphadenoma or in selected cases is a question upon which I should like to have your opinion.

We have now to consider another aspect of the problem, that of the dosage in lymphadenoma. This is not the place for a discussion of details of technique. I will merely ask you to accept the statement that in the great majority of cases of lymphadenoma the masses can be made to disappear by doses which are considerably below the tolerance doses of the skin and other healthy tissues. I have already said that the disappearance of the masses is both macroscopically and microscopically apparently complete, and I personally believe that nothing is to be gained by increasing the dosage in the hope of arresting the inevitable march of the disease. On the contrary, much may be lost by such treatment, since the effect of larger doses on the skin may be such as seriously to limit the application of further treatment when this becomes necessary. I know that, presented with a patient young, and perhaps looking the picture of health, with a single discoverable lymphadenomatous focus, the temptation to do something more energetic than the ordinary treatment, and even to take risks, is great. I submit, however, that if we are to increase the energy of our attack, the increase should be in the direction of multiplying the areas to be treated, rather than in the violence of the attack upon a single area. Moreover, I submit that by an attack limited to the superficial glandular regions, neck, axillæ and groins, we cannot hope to deal adequately with the situation, since it is inconceivable that parts as remote as the neck and groins could be affected without co-existing involvement of the deeper glandular areas.

I may now refer to the efforts that have been made in recent years to improve the results of X-ray treatment in the later stages of the disease. These consist principally in methods of regional irradiation, to which Finzi has applied the term "X-ray bath." These X-ray baths involve the exposure of the whole thorax, or the whole abdomen, or even the whole trunk, to repeated small doses of radiation. They have met with a certain amount of encouragement. Progress has had to

be slow and cautious, but we now know what dosage may safely be tolerated in abdominal and thoracic baths. In the case of trunk baths, however, we are not yet on such sure ground, and I have recently had a case in which an agranulocytosis occurred, which I regarded as being due to the X-ray treatment.

The thoracic baths have proved of great value in cases in which cervical, axillary and mediastinal glands and perhaps, in addition, areas of lung, have been involved; while by means of the abdominal baths results have been obtained in cases which would previously have been regarded as quite hopeless. Unfortunately the results in these last cases have so far proved merely temporary, lasting only for a period of weeks, or perhaps of a few months. Much work, however, still remains to be done in this field, and it is possible that with increase of knowledge of the origin and methods of spread of lymphadenoma, some form of X-ray bath method may become the routine method of treatment.

Dr. F. Parkes Weber said that the inflammatory (infective) nature of Hodgkin's disease was clearly far from being proved. As much, if not more, could be said in favour of a neoplastic theory. He could only touch on some of the main points in the short time at his disposal, and would not of course enter into attempts to explain away the arguments apparently in favour of the disease representing a reaction towards a virus or other infective "agent."

He would define a *neoplastic disease* as one due to proliferation of a cell or more or less a whole system of cells—a cell-proliferation that served no useful purpose and was not conservative in nature—one that did not appear to represent a defensive reaction towards any known virus or other "agent." Neoplastic diseases might, of course, roughly be divided into benignant and malignant ones, but he (Dr. Weber) regarded it as still more important (from the pathological point of view) to divide them into (1) those due to proliferation of a single cell, or small group of cells, and (2) those due to proliferation of more or less a whole system of cells.

The neoplastic diseases of the first of these two classes were represented by the recognized (malignant) carcinomata and sarcomata, and by the various well-known benignant tumours.

The neoplastic diseases of the second class—in which the whole or a considerable part of a system of cells was primarily involved—would include erythræmia, the myeloses (various types of myeloid leukæmia), the lymphadenoses (various types of lymphatic leukæmia), and Hodgkin's disease. Erythræmia, according to this scheme, would represent (in its most typical earlier stages) a benignant neoplastic proliferation of the erythroblastic system of cells; the myeloses would represent, more or less, malignant neoplastic proliferations of the leucopoietic (granulocyto-poietic) system of bone-marrow cells; the lymphadenoses would represent, more or less, malignant proliferations of the lymphoblastic system of cells; whereas Hodgkin's disease would represent, more or less, malignant neoplastic proliferation of the reticulum (in its earlier stages, especially of the lymphatic glands).

One of the most important characters of neoplastic disease was that the cells of which a neoplasm consisted carried on to some extent the special functional and vital activities of the cells from which they had arisen. The reticulum in adults still retained some of its original embryonic power of giving birth to several different types of cells; it could normally (but to a much greater extent as a reaction against known agents) produce reticular cells, endothelial cells, lymphocytes, fibrous tissue, etc. When affected by neoplastic proliferative disease, it produced these various cells and fibrous tissue, and thus all the types of Hodgkin's disease could be explained; they differed from each other only in the relative preponderance of these various types of cells and fibrous tissue—that is to say they differed from each other in the main direction of the "neoplastic trend."

To sum up, he (Dr. Weber) would say that all types of Hodgkin's disease might

be included under the term "reticulomatosis" (for the sake of the present argument he would avoid the indefinite and non-committal term "reticulosis"), but since some other neoplastic diseases (e.g., the reticular type of lymphosarcomatosis) might also be derived from the reticulum, he preferred to speak of "Hodgkin's reticulomatosis."

Dr. Weber did not claim the above explanation (which must necessarily remain an uncertain one) as original, but he thought that the distinction of neoplastic diseases into (1) those resulting from useless proliferation of a single cell or small group of cells, and (2) those due to useless proliferation of more or less a whole system of cells had not yet been properly stressed.[1]

[1] This résumé may be compared with the somewhat more elaborate exposition by Parkes Weber in the *Medical Press*, for March 28, under the title "Erythræmia, the Leukæmias and Hodgkin's Disease as 'Neoplastic Mutations' of Somatic Cells."

Section of Ophthalmology

President—A. C. HUDSON, F.R.C.S.

MEETING HELD AT ST. MARY'S HOSPITAL, MARCH 9, 1934.

Removal of Osteoma from Orbit.—DUNCAN C. L. FITZWILLIAMS, F.R.C.S.

In 1927, Cushing published his experiences of orbito-ethmoidal osteomata with cranial complications,[1] and since that time various views have been upheld as to the best method of dealing with such tumours.

The following is an account of a case that came under my care:—

E. J., aged 51; admitted to hospital, 31.10.32, complaining of giddiness and pain over the left side of the head, with protrusion of the left eye. The pain and giddiness were of several years' duration, but the protrusion of the eye had only been noted for six months and was gradually increasing.

On examination.—There was proptosis of the left eye and the inner canthus was about a quarter of an inch further from the root of the nose than the right canthus. There was some difficulty in lowering the left eyelid; when the left eye moved pain was felt in the upper lid. The pupils were equal in size and intra-ocular tension was normal.

A skiagram showed an osteoma deeply situated in the internal and inferior quadrant of the left orbit.

Mr. Juler examined the eyes and reported: Right vision $\frac{6}{6}$; left vision $\frac{6}{6}$ partly. The right field was full but there was some general contraction of the left.

Operation (8.11.32).—An incision was made from the centre of the supra-orbital ridge to just above the inner canthus of the eye, dividing everything down to the bone. The pulley of the superior oblique was found and the bone chiselled off, with the pulley intact. The periosteum was elevated, as far as possible, from the inner side of the orbit, until the osteoma could be felt. A chisel was introduced and the osteoma loosened from the bone of the inner side of the orbit; it was rocked with forceps until free. It was situated behind the eyeball and the difficulty now was to get it out past the eyeball in the confined space of the orbit. This was done very gradually and with some difficulty, the space being increased by breaking down the thin bone of the inner wall of the orbit. Once the tumour was past the eyeball there was no difficulty. The wound was sutured and drained with a small tube to the back of the orbit, and a firm bandage applied. The actual size of the tumour is seen in the photograph (p. 42).

Next day the drain was removed. Double vision persisted for a month.

Mr. Juler saw the patient again on December 9, and reported slight general contraction of the left field of vision as before, but improvement of the left inward movement of the eye.

R.V. Sph. $-0\cdot25 = \frac{6}{5}$. L.V. Sph. $-0\cdot5$ cyl. $-0\cdot5$ ax. $180^\circ = \frac{6}{6}$.

The removal of an osteoma from the orbit is always difficult, but one principle can be applied to all cases, namely, that the simplest method is the best. If the tumour is small enough to be delivered through the orbit without damage to the eye, this should be the method employed, even if the orbital outlet has to be considerably enlarged by the removal of bone from its inner margin. It is preferable to any of the trans-frontal methods of approach to the orbit which involve the turning back

[1] *Surg. Gyn. and Obst.*, 1927, xliv, 721.

of osteoplastic flaps, the raising of the frontal lobes and the removal of the roof of the orbit. In certain cases, however, when the mass is large or encroaches upon the cranial cavity, the transfrontal route is the only correct method of approach. By this route the wound can be closed either by stitches or fascial grafts, and tears

Tumour removed from left orbit. Actual size.

in the dura, the escape of cerebrospinal fluid into the nose, and the advent of sepsis can be prevented.

If the orbital route is chosen, the operation should be carried out before the tumour has reached such a size as to make its performance difficult.

A similar case was reported by Norman Patterson and Hugh Cairns in the *British Journal of Ophthalmology*, 1931, xv, 458.

Hole at the Macula.—F. A. WILLIAMSON-NOBLE, F.R.C.S.

Miss K. had noticed blurring in the right eye a short time before she came to hospital in January. Vision with correction was less than $\frac{6}{60}$, and there was a central scotoma for colours. Ophthalmoscopic examination showed a reddish area in the macular region, with a white penumbra around it, also some yellowish white dots, and a few crystalline deposits. General examination revealed nothing wrong except some infected teeth. The left eye was normal.

Two septic teeth were removed. There was no history of injury.

Contact Glasses.—F. A. WILLIAMSON-NOBLE, F.R.C.S.

Mrs. H. is a patient who has been wearing contact lenses since February 1932. She has, in the right eye, 13 dioptres of myopia, and 4 of myopic astigmatism, in the left eye, 10 dioptres of myopia and 1 dioptre of myopic astigmatism. The left fundus shows old choroido-retinitis. The right eye, with correction, read $\frac{6}{12}$ and the left eye $\frac{6}{24}$. With a contact lens the right eye read $\frac{6}{12}$ and the left $\frac{6}{12}$ also.

The patient can wear glasses for eight hours, but usually takes them off after four hours.

Discussion.—The PRESIDENT asked whether any members had had experience of the use of contact glasses in cases of cataract extraction with good vision in the unoperated eye.

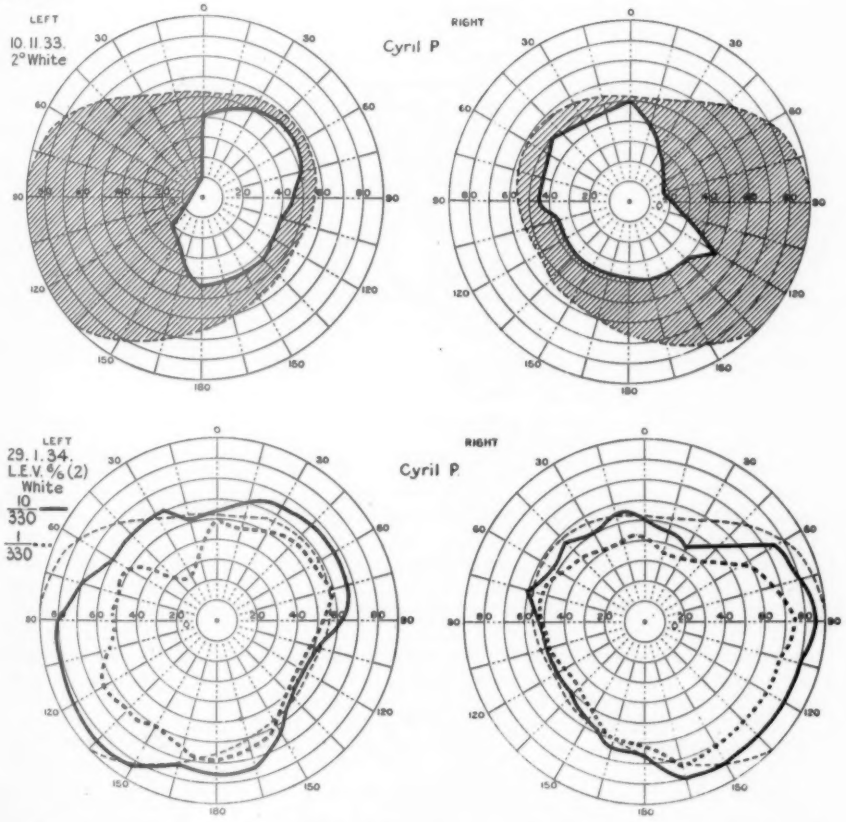
Mr. A. RUGG-GUNN said that such cases really obtained binocular vision. He had a patient, a taxi-driver, who had had both eyes operated upon. He (the speaker) had tried contact glasses in that case, but the patient could not afford to buy them. They gave him binocular vision, with no diplopia. Unilateral cases also obtained binocular vision, often after an interval, but the nature of the refractive error in the sound eye might sometimes prevent it.

Mr. HUMPHRY NEAME said that he had a patient who, at the age of 15, had had a traumatic cataract. When this patient was aged 18, he (Mr. Neame) had tried the effect of contact glasses, but the boy was unable to put the two images together; the difference in their size was about one-eighth of a diameter. He (the speaker) did not know whether that patient had lost the habit of binocular vision, but in his case the procedure did not answer.

Pituitary Adenoma, relieved by Operation.—W. J. ADIE, M.D.

Male, aged 39, attended the Royal London Ophthalmic Hospital on account of defective vision and was operated on by Mr. Julian Taylor at the National Hospital, Queen Square.

History.—For eleven months had had severe left parietal headache daily. This was increased by strain. Vision of left eye noticed to be defective four weeks. Has shaved since the age of 14, but never more than twice a week. Has been becoming pale for twelve months. For twelve months has had a gradual loss of libido.



Examination (November 1933).— Complexion sallow, skin smooth and soft. Hair soft and fair. Right vision $\frac{6}{6}$. Left vision $\frac{6}{24}$. Fields show bi-temporal hemianopia, complete in left, incomplete below in right. Discs normal. Skiagram showed no abnormality of the sella turcica.

Operation (30.11.33).—Right fronto-temporo-parietal flap. Medial to right optic nerve a bluish suprasellar cyst was seen which was incised and evacuated by suction.

Report on tumour (Dr. Greenfield).—The tissue consists of solid masses of cells of slightly elongated shape and with oval nuclei; a few fine blood channels are present in these masses. The tumour appears to be an adenoma of the pars anterior or of the pars intermedia.

Examination (29.1.34).—Right vision $\frac{6}{6}$. Left vision $\frac{6}{6}$ partly. Headaches gone. "Feels a different man." Discs normal. Visual fields much improved; the right is almost full, the left has some temporal loss, mostly in upper quadrant.

Discussion.—The PRESIDENT asked what was the prognosis in such a case as this, and whether any such measure as the application of radium was suggested as a safeguard against recurrence.

Mr. F. A. JULER said he understood that there was no relapse in these cases.

Unilateral Proptosis. ? Graves' Disease.—F. A. JULER, F.R.C.S.

Patient, aged 34, female.

History.—Right eye noticed for three years to be prominent, gradually getting worse. No other complaint. No headache. No pain.

Present condition.—Right eye proptosis 3 mm. Ocular movements full. Marked retraction of upper lid. No diplopia. Visual field full. Fundus normal. No feeling of resistance on pressure of globe backwards.

Right vision $+ 0{\cdot}75 + 0{\cdot}50 \searrow 110 = \frac{6}{6}$.
Left vision $+ 0{\cdot}25 + 0{\cdot}50 \swarrow 45 = \frac{6}{6}$.

General health good; well nourished, not nervous, no palpitation. Pulse steady (64-80), no tremor.

Special investigations.—Wassermann reaction negative after provocative dose of novarsenobillon (0·3 grm.). Skiagram of orbit and sinuses, negative. Basal metabolic rate (by three methods) is within normal limits. No signs of hyperthyroidism.

? Optic Nerve Tumour.—F. A. JULER, F.R.C.S.

Female, aged 36, married. Was seen first on October 31, 1933.

History.—Left eye painful, and headaches around the left side for twelve months. Left vision failing for twelve months.

Condition on examination.—Right vision $\frac{6}{5}$; left vision $\frac{6}{12}$; cyl. $+ 0{\cdot}25$; ax. $10° = \frac{6}{9}$. Tension normal. Left disc paler than right. Left eye proptosis 3 mm. Movements full. No bruit. No palpable tumour. Feeling of resistance in orbit on pressing the globe backwards.

Special investigations.—Wassermann reaction negative. Maxillary antra dark. Bilateral antrostomy revealed no pus. X-ray report of sphenoidal area negative. Left field full, but paracentral scotoma present in temporal field, close up to fixation point.

Course.—During three and a half months the headache and vision have varied only slightly. Since the middle of December the left pupil has been larger than the right, but both react. The proptosis is possibly a little greater.

Treatment.—Potassium iodide.

Diagnosis.—? Optic nerve tumour. ? Meningioma.

Meningioma of the Optic Nerve.—F. A. JULER, F.R.C.S., and W. D. NEWCOMB, M.D.

Female, aged 40. Sudden failure of vision two years ago, with increasing pain and proptosis for five months. Fundus showed widespread greyish oval area at posterior pole.

June 1933.—Exenteration of globe and posterior part of orbital contents. Skiagram of optic foramen showed it to be of normal size.

July 1933.—On account of continued pain, Mr. A. Dickson Wright explored the anterior fossa and found the optic nerve of normal size.

Report on tumour.—Meningioma of optic nerve. The tumour consists of cells which vary from plump oval to elongated spindle ; some in solid masses, others in columns ; in places vacuolated and forming narrow spaces. It is not a malignant tumour so far as can be seen from the specimen. It is unlikely to have been completely removed.

Microscopic examination of the eye shows that there is no intra-ocular growth and that the fundus changes are due to an œdematous coagulum.

Glaucoma from Vitreous in Anterior Chamber relieved by Trephining.—F. A. JULER, F.R.C.S.

Male, aged 52. Came on 12.11.33, with a history that a piece of iron had struck his left eye on the previous day.

Condition on examination.—Right vision $\frac{6}{9}$. Left vision $\frac{4}{60}$. Tear of conjunctiva at 12 o'clock. Corneal œdema ; tension ; vitreous in anterior chamber. Vitreous clear. Fundus normal. Tension remained high in spite of various treatments.

December 4, 1933.—Left posterior sclerotomy.

December 13, 1933.—Left trephine with complete iridectomy.

January 3, 1934.—Left eye slight injection. Tension normal. Vision $\frac{6}{60}$, not improved. Vitreous in anterior chamber. Lens dislocated down and in, slightly hazy. Details of fundus not well seen.

February 8, 1934.—Tension normal. Eye white.

March 1, 1934.—Tension raised, no pain. Lens hazy. Vision $\frac{1}{60}$.

The PRESIDENT said that some years ago he had shown a similar case, with fulminating attacks of glaucoma, which had been treated by corneo-scleral trephining. Vitreous was not lost, and the operation turned out very well. Had Mr. Juler's patient lost vitreous? [Mr. JULER : No.]

Six Cases of Squint, demonstrating the value of Orthoptic Treatment.—E. E. CASS, M.B.

I.—*Left divergent strabismus.* Aged 11 ; deficiency of convergence, improved by training.

December 1933.—Right eye $\frac{6}{6}$. Left eye $\frac{6}{6}$. Emmetropic. No convergence on near.

January 10, 1934.—Fusion training began. Child had no fusion. Angle of squint 14° divergent.

February 2, 1934.—Began to fuse at − 15°. Has now some convergence. With − 3 spheres can fuse at 0°.

II.—*Divergent strabismus.* Aged 11 ; excessive divergence, improving during training. Right c. + 0·5 = $\frac{6}{6}$. Left c. + 0·75 = $\frac{6}{6}$. Convergence perfect. Divergence only on looking into distance. Angle of squint 4°.

December 1933.—Fusion training begun. No fusion.

January 24, 1934.—Fusing at − 16°.

III.—*Left convergent strabismus.* Aged 12.

Treatment.—Left recession and fusion training.

History.—Squinted since age of 5, following pneumonia.

Angle of squint.—24° with glasses.

Right $\frac{+1\cdot5}{+1\cdot0 \text{ ax. } 105^\circ} = \frac{6}{5}$. Left $\frac{+3\cdot5}{+1\cdot0 \text{ ax. } 120^\circ} = \frac{6}{12}$. 5 mm. of recession performed on left eye. Eyes straight with glasses after operation. Child had no fusion, and it was four months before he could fuse.

IV.—*Left convergent strabismus.* Aged 4½ years.

Cured by training. Angle of squint with glasses 15°.

History.—Squinted a few months following whooping-cough. First seen February 1930.

May 1933.—Right $\frac{+3\cdot0}{+0\cdot5 \text{ ax. } 90^\circ} = \frac{6}{6}$. Left $4\cdot0 = \frac{6}{9}$. Angle still 15°. Fusion training begun.

Discharged after five months with eyes straight and fusion perfect.

V.—*Left convergent strabismus.* Aged 9 years.

Cured by training. First seen September 1932. *Left angle* with glasses 20°.

May 1933. Right c. $+4\cdot5 = \frac{6}{9}$. Left c. $+5\cdot5 = \frac{6}{18}$. Doyne's disc to right eye constant.

September. Left eye with glasses $\frac{6}{6}$ partly. Fusion training begun. Had no fusion.

In a month could fuse nearly everything with axes parallel.

December 1933. Child's eyes straight with glasses and fusion perfect.

VI.—*Left internal strabismus.* Aged 9 years.

Cured by training.

History.—Squinted when tired; becoming constant.

March 1932. Right $+0\cdot25 = \frac{6}{5}$. Left $+0\cdot5 = \frac{6}{5}$. Angle with glasses 8°. Some degree of fusion.

In April child had measles, and in July, whooping-cough.

Discharged November 1932, with eyes straight.

Unexplained Bilateral Proptosis.—E. F. KING, F.R.C.S., and T. R. HILL, M.D.

W. G., male, aged 50. First seen as out-patient at the Royal Eye Hospital, in August 1933, complaining of diplopia of four months' duration. The condition has not changed materially since that date.

Examination shows œdema of lower lids, proptosis, chemosis and congestion of conjunctival vessels, more in the right than the left eye. The right eye is convergent with gross loss of lateral movement; in the left eye there is some loss of lateral movement but not so marked as in right eye. On palpation there is a sensation of solid œdema, and the globes cannot be pushed back into the orbits. Pupils equal, and react to light and accommodation. Tension normal. Sclerosis of retinal vessels, otherwise fundi normal. Right vision $\frac{3}{60}$, not improved; left vision $\frac{6}{36}$, not improved. Fields full, blind spots normal.

General examination (at West End Hospital for Nervous Diseases).—Ear, nose and throat normal. Urine normal. Wassermann reaction normal. Basal metabolic rate not raised. Some evidence of general arteriosclerosis with subnormal blood-pressure. Skiagrams of skull show slight calcification of choroid plexuses in lateral ventricles. Skiagrams of orbits normal. No evidence of general systemic disease.

Congenital Abnormality affecting Iris and Lens of Right Eye.—A. C. HUDSON, F.R.C.S. (President).

Male, aged 11½ years. Adhesion at three points of anterior surface of lower and inner part of iris to back of cornea. Extensive lens opacity, with pyramidal anterior capsular cataract, adherent by its apex to back of cornea.

Right eye.—Vision, bare perception of light, with defective projection of light from nasal field.

Left eye.—Healthy. Vision $\frac{6}{6}$, with − 2·75 D. sph.

Hypotony after Sclero-corneal Trephining.—A. C. HUDSON, F.R.C.S.

M. E., female, aged 46.

This case was shown on October 13, 1933,[1] and is brought forward again to show the result of further treatment.

3.2.34.—Right vision $\frac{6}{36}$, with + 5 D. sph. + 1 D. cyl. 70°.

25.2.34.—Cystoid scar in cornea punctured with diathermy needle. Conjunctiva incised throughout upper third of limbus, freely dissected from sclerotic, brought down over upper part of cornea and fixed with two sutures.

6.3.34.—Right, Schiotz tension, 3 mm.

7.3.34.—Right vision, with + 2 D. sph. + 1·25 D. cyl. 30° = $\frac{6}{9}$ partly.

Œdema of nerve-head has subsided.

POSTSCRIPT (16.5.34).—Right, Schiotz tension, 7 mm.

Tonic Pupils.—A. LISTER, F.R.C.S. (introduced by Mr. P. G. DOYNE, F.R.C.S.).

P. H., female, aged 14 years and 9 months.

About twelve months ago the patient noticed that the left pupil was unusually large. It has been so practically ever since, although it varies in size to some extent during the course of the day. It is always largest when the patient wakes in the morning.

The right pupil is regular and reacts well to light and on convergence.

The left pupil when first seen was three-quarters dilated and appeared to be fixed. After about thirty seconds' exposure to light it began to contract slowly, and finally contracted to the size of the other pupil. When the light is removed it very slowly dilates again. It behaves similarly after maintained convergence.

There is no abnormality of accommodation. Fundi and media are normal. Movements are full.

Vision: Right $\frac{6}{5}$ and J 1; left $\frac{6}{9}$ and J 1, slight hypermetropic astigmatism.

Tendon reflexes all present.

Unilateral Lamellar Cataract.—C. SHAW, L.R.C.P., M.R.C.S. (introduced by F. A. JULER, F.R.C.S.: Case shown by A. LISTER, F.R.C.S.).

W. U., male, aged 17. Attended the Royal London Ophthalmic Hospital under Mr. F. A. Juler 12.2.34, complaining of poor vision in left eye, which he had noticed for four or five years, though he and his father think he has had it since birth. The father's only explanation for it is that his son was born during a Zeppelin raid; the labour was prolonged and forceps were used. There is no other suggestion of injury.

Examination showed: Right vision $\frac{6}{12}$; left vision, counting fingers at 1 metre. Pupils equal and active. Tension normal. Right with − 0·50 sph. = $\frac{6}{6}$ under homatropin and cocaine. Right media and fundus normal. No right lenticular opacities were seen with the slit-lamp. Left eye shows typical lamellar cataract. No family history of cataract; no history of injury.

Teeth show no evidence of defective enamel.

[1] *Proceedings*, 1933, xxvii, 147 (Sect. Ophthal., 1).

Diplopia from Paresis of the Left External Rectus Muscle; Relief following the Operation of Advancement and Resection of the Muscle.—L. H. SAVIN, F.R.C.S.

The patient is an attendant at a mental hospital. In January 1933, a dementia præcox patient suddenly ran amok. The attendant received a blow in the left eye. Blood poured from a cut in the eyebrow; and on wiping this blood away he was astonished to see that the clock appeared to be double. This diplopia persisted.

On examination (November 1933).—Paresis of left external rectus muscle with diplopia when looking ahead or to left. The left side of the face occasionally showed signs of spasm. The fundi showed signs of an old and diffuse chloroidoretinitis. Right vision $\frac{6}{6}$, left vision $\frac{6}{12}$ with glasses.

Neurological examination by Dr. J. Purdon Martin showed no other abnormalities. The Wassermann reaction was negative in blood and cerebrospinal fluid. No signs suggesting tuberculosis were found. It seemed probable that the nerve lesions were traumatic in origin, perhaps involving the sixth and seventh nerves near the lower border of the pons. X-ray examination was negative.

Operation 13.1.34.—Under cocaine and novocain anæsthesia, a full advancement of the left external rectus was performed with resection of the terminal centimetre of the tendon.

Result.—Diplopia cannot now be elicited. With the Maddox rod test there is 4° of right hyperphoria. On examination with the synoptophore the patient suppresses in the left eye.

A Case of Diplopia from Paralysis of the Right Superior Oblique relieved by Recession of the Right Superior Rectus.—L. H. SAVIN, F.R.C.S.

The patient is a fly-weight boxer, formerly of considerable renown ("Boy Walley, of Singapore"). In June 1932, he received a heavy blow in the face during the third round of a fight. He immediately saw double. This diplopia persisted, preventing his judging distances, and stopping his boxing. In August 1933, he had diplopia corresponding with paralysis of the superior oblique in the right eye.

Right vision $\frac{6}{6}$, left vision $\frac{6}{12}$. His left eye showed vitreous opacities. He wore a shade to avoid diplopia. An old hæmatoma was noted in the left ear. At this late date no bony injury was seen in a skiagram. Wassermann was negative.

Operation.—In September 1933, the right superior rectus was retired under cocaine and retrobulbar novocain anæsthesia. Two mattress sutures of silk were passed through the superficial sclera about 3 mm. behind the original muscle insertion, then through the freed distal end of the muscle and loosely out through the conjunctiva. The muscle was allowed to slip back a considerable distance behind its original insertion. The loose sutures were then tightened till the horizontal red line of a Maddox rod before the left eye appeared to pass through a lamp held six feet above the patient's feet as he lay down. The sutures were then tied.

Result.—After some transitory vertical diplopia the patient has now recovered single vision and discarded his shade. The Maddox rod still shows 5° of right hyperphoria; but this does not seem to cause him discomfort.

Infantile Cerebro-macular Familial Degeneration: Amaurotic Family Idiocy (Tay-Sachs).—VICTOR B. PURVIS, D.O., D.O.M.S. (by request of R. AFFLECK GREEVES, F.R.C.S.).

H. L., female, aged 11 months.

History.—Four months ago the child was taken to the Hospital for Sick Children, Great Ormond Street, because she was "slow at picking things up," and the case was there diagnosed as one of Tay-Sachs' disease. At that time the child

appeared to be healthy generally, but has since then gradually become weaker and irritable, and lately has had some digestive trouble.

24.2.34: Attended the Royal London Ophthalmic Hospital under Mr. Affleck Greeves.

On examination.—Now unable to sit up; moderate spasticity of extremities; appears to be able to see, but not well. Pupils equal and active; both fundi show the typical picture of infantile cerebro-macular disease and are equally affected. The illustrations in Waren Tay's original article might well have been drawn from this case. The maculæ stand out as dull red spots, about a third of a disc in size, surrounded by a white opaque area which extends to midway between the macula and the disc and which forms an approximate circle around the macula. The optic discs are not grossly affected yet, but there is slight though definite general pallor.

Family history.—Third and youngest child of Jewish parents, who are not consanguineous. Two siblings; eldest sister died of Tay-Sachs' disease at age of 2 years 3 months; second sister alive, aged 3 years; no abnormality. All other members of a prolific family have been free from this disease for three generations, and it is not possible to trace the story further back.

This case of a familial disorder with recessive inheritance is shown as a perfect example of a comparative rarity, with onset at the age of about six months, in the course of progressing to the usual fatal termination.

Irradiation and Cure of Epithelioma of Lid by Radium, with Production of Late Radium Cataract.—VICTOR B. PURVIS, D.O., D.O.M.S. (by request of R. AFFLECK GREEVES, F.R.C.S.).

N. J. S., male, aged 52, printer.

History.—First attended the Royal London Ophthalmic Hospital in September, 1930, under Mr. Affleck Greeves, with the complaint of a swelling on the left upper lid of about two years' duration. It had begun as a wart.

On examination. (20.9.30).—Tumour of left upper lid, about 2 by 1½ cm.; infiltrating lid throughout; broad base and raised about 1 cm. above normal surface-level of lid (fig. 1). Small piece excised for section.

Before radium applications.

After radium applications.

2.10.30: *Pathological report on micro-section.* (Mr. H. B. Stallard): Epithelioma with cell nests.

7.10.30: Patient transferred to the Middlesex Hospital for radium therapy. 120 hours' continuous surface application of radium element screened to produce pure gamma irradiation, to ensure adequate and uniform penetration and at the same time avoid necrosis. The dose was large enough to be effective and also to avoid the possibility of radium tolerance.

12.10.30: Radium removed; container found to have slipped down off upper part of tumour.

4.11.30: Already marked improvement; slight burn of part of tumour.

17.11.30: In view of the slipping of the first application, with the possibility that the upper part of the tumour was not adequately irradiated, it was considered necessary to give further irradiation, although the first application was originally intended to be the full dose. Radium was therefore reapplied to the upper part of the tumour for five hours. (Surface application: gamma irradiation.)

18.11.30: Radium re-applied for the same reason and to the upper part for two and a half hours. (Surface application; 30% beta irradiation.)

2.12.30: Tumour almost disappeared; fairly severe reaction and marked conjunctivitis.

23.1.31: No sign of growth (fig. 2).

Case under continual observation until 15.11.32 and no abnormality noted.

18.7.33: Came up complaining of four months' history of mist over left eye which had quickly become gross. On examination.—A practically mature left cataract was found, intumescent, dense and of diffuse opacity. No sign of lid tumour. Right eye normal.

Present condition (March 1934).—Left eye: Vision, L.M.O. at 25 cm., projection excellent; no corneal defect; mature cataract. No sign of recurrence or metastases of lid epithelioma. Right eye: Nothing abnormal; lens clear.

This case illustrates the treatment and cure of epithelioma of the eyelid with radium alone. It was considered that radium should be given a trial, rather than excision, as, owing to its extensive infiltration by the tumour, the whole of the lid would have had to be removed. The radium was applied on three occasions in varying amounts and for varying duration as a surface application over a period of six weeks. The total irradiation amounted to 4,895 mgm.-hours. Within three and a half months of the first application of radium, the tumour had disappeared. Now, more than three years later, there is no sign of recurrence. These is little or no deformity as a result of the irradiation.

The case also demonstrates the occurrence of late radium cataract. The patient was seen two years after irradiation and no abnormality was noted and there was no loss of visual acuity. Two years and three months after irradiation, there was a sudden gross loss of visual acuity and on examination two years and eight months after irradiation a practically mature cataract was discovered.

I am indebted to Mr. Affleck Greeves for kindly asking me to show these cases and to Dr. F. G. Nicholas for radiological details.

Discussion.—Mr. J. D. M. CARDELL asked what screening and protection were afforded during the irradiation.

Mr. H. B. STALLARD said that the use of small doses of radium in the form of radon seeds and of unscreened radium for short periods of time was found not to cause irradiation cataract when used in the vicinity of the eye. He had seen a number of cases treated by inserting radon seeds into the lids and by the use of unscreened radium applied for an hour or so directly on to the conjunctiva, and in these cases there had been no sign of irradiational cataract during the last five years, within which time these cases had been kept under observation. The β rays were employed mainly when unscreened radium was used.

Probably the deeper penetrating γ rays damaged the capillaries of the ciliary body and disturbed the nutrition of the lens and these rays reached the ciliary body when radium needles and massive doses of radium were applied near the eyes.

Dr. PURVIS (in reply) said that he was appending a list of details. It was practically impossible to protect the eye. Even if it were possible to find a patient who would endure a filter between the lid and the globe, not to mention the probability of the filter itself damaging the cornea, the eye would then receive secondary irradiation which would be more dangerous than the primary. A second filter would therefore have to be interposed between the first filter and the eye in order to absorb the secondary irradiation and there was not sufficient room in which to do this.

DETAILS OF RADIUM TREATMENT.

Radium containers	7.10.30	17.11.30	18.11.30
Number	8	9	1
Strength (mgm. Ra.el.)	2·5	5	8
Intensity (mgm. per sq. cm.)	3·3	15	5
Wall thickness (mm.)	0·3 Pt.	0·3 Pt.	0·2 Ag.
Extra filters (mm. of stent)	7·5	3	0
Total milligrams Ra.el.	20	45	8
Duration (hours)	120	5·1	2·5
Mgm.-hours Ra.el.	2,400	2,295	200

Total irradiation = 4,895 mgm.-hours.

Lower Bulbar Conjunctival Neoplasm (? Papilloma or Angeioma) with Upper Subtarsal Sulcus Papilloma.—H. H. SKEOCH, F.R.C.S.

Patient, H. H., aged 23 years, under care of Mr. R. Affleck Greeves, attended hospital out-patient department 24.2.34. Right vision $\frac{6}{6}$, left vision $\frac{6}{6}$; with lower bulbar conjunctival neoplasm—? papilloma or angeioma—and upper subtarsal papilloma of right eye. Lower bulbar conjunctival tumour first noticed, nine months ago, growing in a horizontal fringe-like manner from lower bulbar conjunctiva midway between limbus and lower fornix to a lateral extent of 1·5 cm. Edge of fringe flattened fanwise upwards on bulbar surface by lid action and overlapping lower margin of cornea. Tumour tissue was of conjunctival transparency, and nourishing blood-vessels were clearly visible, branching out fanwise radially from centre of stalk below.

The growth did not interfere with vision and occasioned no particular discomfort.

Upper growth first noticed one month ago when it had become large enough to show beneath centre of upper lid. Eversion of lid showed a papilloma growing on a slender stalk from the subtarsal sulcus. The stalk branched out in a floriform manner into several separate pink petal-like shapes. In the ensuing six weeks before its removal by excision it was considered to have grown appreciably in size.

Pathological section showed a typical papilloma composed of stratified squamous epithelium with keratinization on a core of well-vascularized connective tissue.

Postscript.—The bulbar conjunctival growth was excised by Mr. Affleck Greeves. A microscopic section showed greatly thickened and vascularized conjunctival epithelium, described in the pathological report as "epithelial hyperplasia," but in my opinion appearing to be consistent with the idea of an unusual form of conjunctival papilloma.

Xerosis.—FREDERICK RIDLEY, F.R.C.S.

Patient, male, aged 27, has noticed four small dry patches adjacent to the cornea in the palpebral fissure for twelve months. These have given rise to no symptoms. The appearance is that of "xerosis," but repeated bacteriological investigation has proved negative, or has produced only isolated colonies of *Staphylococcus albus*

and *B. xerosis*. Smears have shown no organisms. There is no vitamin deficiency, no night blindness and no significant family history. The condition appears to be stationary, and the only abnormality discovered is a deficiency in the protein of the tears, which contain only 10% of the normal amount.

It is suggested that the drying of the patches of conjunctiva is attributable to the protein deficiency giving rise to defective film formation, so that the xerotic areas of conjunctiva are exposed.

Section of Therapeutics and Pharmacology

President—J. H. BURN, M.D.

[*March* 13, 1934]

Derived Antigens as a Means of Studying the relation of Specific Combination to Chemical Structure

By J. R. MARRACK, D.S.O., M.C., M.D.

NATURALLY occurring antigens have the disadvantage, for the study of the relation of specificity to chemical structure, that their constitution is incompletely known and that very little is known of the arrangement of the constituent units in their molecules. Slight chemical differences may be detected between two antigens – such as the serum albumins of two different species, but it is not possible to decide what is the essential difference which determines that the one will act with the homologous antiserum and that the other will not. Even the specific polysaccharides, whose constitution is better known, do not provide a range of variations of structure convenient for the study of the relation of constitution of specificity.

This difficulty can be overcome by the use of derived antigens. By attaching known chemical groups to proteins in various ways antigens are formed the specificity of which is determined by the groups so attached. The most convenient method of attachment is by an azo-link.

A substituted aniline (in which R may be an atom or radicle, and need not be in the para position) can be diazotized and coupled to the tyrosin and histidin units in a protein, forming an azo-dye. If a rabbit is immunized with such a compound its serum will give a precipitate more or less specifically with a protein to which a diazotized substituted aniline has been coupled. Further this formation of a precipitate is inhibited by the presence, in excess, of such simple chemical compounds as the same substituted aniline diazotized and coupled to phenol, by the substituted aniline itself, or even by simpler compounds containing the substituent group R, of the aniline. This phenomenon is explained by the theory that the antibody molecule contains sites which combine specifically with "R" or with "R" attached to a benzene ring; when simple "R" compounds are present in excess they occupy all these sites on the antibody, and prevent the access thereto of the protein compounds. This combination of simple "R" compounds with antibody has also been demonstrated directly. One stage of the reaction between such derived antigens and the corresponding antibodies can therefore be considered to be *a specific combination between antibodies and chemical groups of known structure*. Using the azo-method the nature and composition of the "R"s can be varied very widely, and hence the effect of a great range of chemical variations on specific combination can be studied. Other methods give similar results but are less convenient; that recently introduced by Hopkins and Wormall (1933), the formation of substituted ureas by a reaction between free $-NH_2$ groups and phenyl-isocyanate may prove valuable. It has the advantage that it is not necessary to expose the protein to a strongly alkaline reaction.

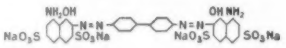
The relation of specificity to chemical structure.—When the "R"s of the substituted aniline employed are relatively simple and inert (e.g. -CH-, Cl, -Br, -I) the specificity is determined by the position of the "R" in the benzene ring, rather than by its structure. Thus the antibody [1] to p-$Cl.C_6H_4.NH_2$ reacts equally with the antigens in which the place of -Cl is taken by $-CH_3$, -I or -Br; but less strongly with the antigens in which the -Cl is in the ortho or meta position. These "R"s therefore behave as inert projections on the benzene ring. When the "R"s are more reactive the specificity is determined by the nature of the R. Thus, $H_2O_3As.C_6H_4.NH_2$ antibody will not react with $HO_2SC_6H_4NH_2$ antigen. The position of the "R" is of less importance; ortho-amino-benzene-sulphonic acid antibody gives precipitates with both o-amino-benzene-sulphonic acid and m-amino-benzene-sulphonic acid antibodies. With these more active groups the benzene ring is beginning to serve merely as a link. This also is shown in the case of p-amino-benzene-arsinic acids by the fact that the reaction of antibody and antigen is inhibited by arsinic acid. When more complex groups are used it appears that spatial arrangement plays an important part in determining specificity. Specific differences were demonstrated (Landsteiner and van der Scheer, 1928) between the antigens prepared with the dextro- and lævo- isomers of phenyl (p-amino-benzoyl-amino)-acetic acids. A sharper distinction was demonstrated between the antigens prepared with the dextro- and lævo- isomers of tartranilic acids. In these and the subsequent examples it is obvious that the benzene ring is merely a means of attaching the essential group to protein. The remarkable effect of a small spatial change is shown by the high specific difference between p-amino-phenol-β-glucoside and p-amino-phenol-β-galactoside (Avery and Goebel, 1929) which differ only in the arrangement of -H and -OH at the No. 4 C atom of the hexose. A less sharp difference was found by Avery, Goebel and Babers (1932) between α- and β-glucosides which differ in the arrangement at the No. 1 C atom. Apart from their purely theoretical bearing these experiments are interesting in relation to the specificity of naturally occurring polysaccharides. Thus the polysaccharide of Type III pneumococcus is built up of an aldobionic acid formed from glucose and glucuronic acid. The rather different polysaccharide of gum arabic is built up to an aldobionic acid formed from galactose and glucuronic acid. The experiments of Landsteiner and van der Scheer (1932) with dipeptides as determinant groups may have a similar bearing on the specificity of natural proteins. They immunized with such compounds as p-amino-benzoyl-glycyl-leucine, and found that specificity was mainly determined by the terminal amino-acid but affected to some extent by the amino-acid next to it. The specific character of natural proteins may, in the same way, be determined by the nature of the amino-acids at or near the surface of the molecule.

Nature of the specific combination.—It is difficult to conceive that the type of specific combination described above is due to chemical combination between the atoms of the molecules concerned. This type of reaction could hardly account, for example, for the equivalence of p-chlor-amino-benzene and p-methyl-amino-benzene. It is necessary to consider the possibility that the combination may be due to the forces which act between molecules and to discuss whether this idea is compatible with the high degree of specificity found. The familiar purity of crystals shows that the binding together of molecules may be very specific. As a rule only one type of molecule is built into a crystal. If, however, a foreign molecule conforms sufficiently well, in dimensions and in the distribution of electric fields on its surface, to the principal molecules of a crystal, it also may be built into the crystal lattice. In this way thiophene can be built into a crystal of benzene. If a foreign molecule only conforms in part to the molecules of a crystal it may be built on to

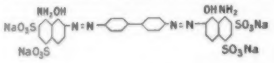
[1] It is covenient to denominate antigens and the corresponding antisera by the substituted anilines from which the antigens were synthesized; or even on occasions, by the corresponding "R".

the surface of the crystal. For example, urea molecules can be built on to the cubic faces of ammonium bromide crystals, the bromine ions fitting into depressions between the urea molecules which are spaced at suitable intervals.

Specific differences may be found in such surface adsorption, which recalls the specific combination of immunological reactions. The dye



is adsorbed on the cube faces of potash alum, whereas the dye



which differs only in spatial arrangement is not adsorbed (France, 1930). The dextro- and lævo- forms of the dye obtained by coupling diazotized phenyl (p-amino-benzoyl-amino)-acetic acid to dimethyl-aniline are unequally adsorbed by wool (Ingersoll and Adams, 1922).

From this standpoint, groups which are similar in dimensions and electrical fields should be equivalent immunologically. Erlenmeyer and Berger (1932) have shown that this is the case with the groups -CH_2-, -O-, and -NH-. The antigens formed from $C_6H_5CH_2C_6H_4NH_2$, $C_6H_5OC_6H_4NH_2$ and $C_6H_5NHC_6H_4NH_2$ are immunologically equivalent. The similarity of the dimensions and electric fields of these three groups is shown by physico-chemical considerations.

Specific combination in other types of biochemical reaction. — A specific combination of enzyme and substrate appears to be the first stage of an enzyme reaction. Idiosyncrasies to various substances and the specific actions of drugs probably depend on similar specific combinations. The reactions with derived antigens afford the most convenient means for the study of the nature of this specific combination. The reacting substances can be isolated more completely than can those involved in the reactions of drugs. It is not possible to produce appropriate enzymes to act on compounds we wish to study; it is only possible to use such enzymes as are naturally available. The examples given indicate the possibilities which the use of derived antigens may afford in the study of specific combination. The studies have so far not been extensive. Although the method now mainly employed was introduced by Landsteiner and Lampl seventeen years ago, it has been fully exploited only during the last few years.

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A Note on the Treatment of Asthma

By A. G. AULD, M.D.

THE peptone that I have been using for the past two years is Witte's special peptone 30, which he brought out in collaboration with a German University in 1931. It is the best peptone for injection that I have tried. It does not require to be given intravenously, but should be given intramuscularly in the upper gluteal region in a five per cent. aqueous solution. No alkali is necessary. It may produce a slight reaction at first, but if the patient gets a dose of adrenalin at the same time, this may often be avoided. I have not found it necessary to produce any pyrogenic reaction.

The action of this peptone is undoubtedly strengthened by a concurrent injection of bismuth. How this acts, it is difficult to say, but I made some observations on the subject last year. It seems to cause catalysis of the peptone in the reticulo-endothelial system and also to stimulate the immunizing power. The hydroxide of bismuth may be used, but the metal itself (B.P.) is very good, 1 c.c. being given each time the peptone is injected. The dose of peptone depends largely on the skin reaction of the patient, beginning ordinarily with 0·3 c.c. and going on by six injections twice, or even thrice, a week up to 1·5 c.c. After this it may be given by increases of 0·3 c.c. to 2·5 or 3 c.c. for two or three weeks, when it is given once a week (2·5 c.c.) for a few weeks, and then once a fortnight for two months.

Serum peptone.—Dale and Kellaway showed, in 1922, that the normal serum of a guinea-pig, protected against anaphylaxis in the guinea-pig, if sufficient time were given. Acting on this, I tried the serum of the patient mixed with peptone.

Draw off about 4 or 5 oz. of blood into an Erlenmeyer flask (about 6 in. wide at the bottom and 1 in. at the summit); a tube should not be used. Lay aside the flask for two days, when, if the patient has not taken food for four hours previously, a fine effusion of serum has occurred. If the flask is only permitted to stand for one day, the effusion is less, and is somewhat bloody. I have tried centrifuging the blood and taking off the serum at once, but with no different result. The serum is now decanted or pipetted into a tube and placed in the incubator at 37° to 40° C. with 5% of peptone and the requisite quantity of chloroform. Turn off the light in about two to three hours, and leave the tube in the incubator till next day. On removing it, it will be found that the peptone has entirely dissolved, leaving a clear mixture, with but a trace of substance at the bottom. If the patient objects to having the blood removed, use the serum peptone from another case somewhat similar.

When I began to use this serum peptone, I gave it intramuscularly in the same strength as the peptone itself, together with bismuth, but I found lately that it could be given in about double the quantity without producing the reaction of ordinary peptone. Novy and De Kruif found that guinea-pigs, given their own serum with peptone, could stand as much peptone as would prove fatal without the serum. This is an important finding, and permits us, if necessary, to use more serum than the usual amount when added to the peptone. The importance of this serum peptone lies in the fact that the peptone is so united to the serum that it takes longer to act, and together they act more efficaciously than the watery solution.

Copper Therapy in Nutritional Anæmia

By J. C. Hawksley, M.D.

The action of copper in promoting hæmatopoiesis has been extensively studied by Hart, Steenbock, Elvehjem and Waddell [1]. These workers observed that it was impossible to cure rats previously rendered anæmic with milk feeding, by the administration of chemically pure iron salts, but that the addition of small quantities of copper effected cure. These experiments have been repeated by various workers, some of whom maintain that other metals act in this way, though less effectively than copper. Parsons and Hickmans [2] regard the work of Hart, *et al.*, as amply confirmed.

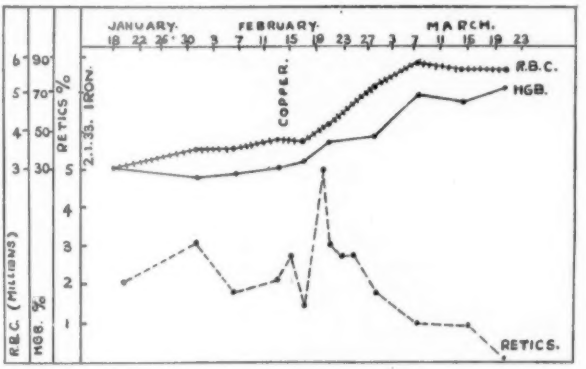
The effect of copper is in part explained by experiments of Elvehjem and Sherman [3]; they noted that in milk-anæmia of rats, pure iron when administered was absorbed and stored in the liver and spleen; it was not mobilized for hæmatopoiesis, except in the presence of copper. Elvehjem and Schultze [4] demonstrated that a typical reticulocyte response only occurred under these conditions in the presence of adequate iron and copper together.

In the human infant the storages of iron and of copper have points of resemblance; the bulk of both elements, present in the body at birth, is laid down in the last three months of intra-uterine life, and there is a similar fall in both between early infancy and weaning [5, 6]. This makes possible the assumption that nutritional anæmia may in some cases be due to copper deficiency, similar to the common iron deficiency type, and also that in some cases both factors may be involved. Two methods of demonstrating the action of copper in nutritional anæmia have been employed; one consists in using iron and copper therapeutically together, and observing the effect of this when compared with controls on iron only. The other consists in treating all nutritional anæmias with iron only, observing whether this cures all cases, and if it does not, supplementing the iron with copper in instances where iron alone has failed.

Josephs [7] gave copper and iron in one series of cases and iron only in another. He found that a more rapid recovery occurred in the former group. Caldwell and Dennett [8] obtained similar results. On the other hand, no differences were observed between the two methods by Mackay [9], who, however, had only used it on a few cases, and suggested that cases might exist in which it was necessary to use copper. Lottrup [10] found copper ineffective, but only quoted two cases.

Parsons and Hawksley [11] in a series of cases of nutritional anæmia found three in which iron was unable to effect cure. In each case, using copper as a supplement, cure was obtained. As these were the only three cases where copper was employed they had no failures. Neither they nor Josephs were able to demonstrate any reticulocyte response similar to that obtained in rats by Elvehjem and Schultze [4] when iron and copper were given in adequate quantity.

A further case, in which copper deficiency was observed, has recently been treated at the Hospital for Sick Children. Administration of iron over a period of six weeks was ineffective, while the addition of copper produced a brisk reticulocyte kick, followed by return to normal of the erythrocytes and hæmoglobin (Graph 1). The diet remained unchanged both in this case and those quoted by



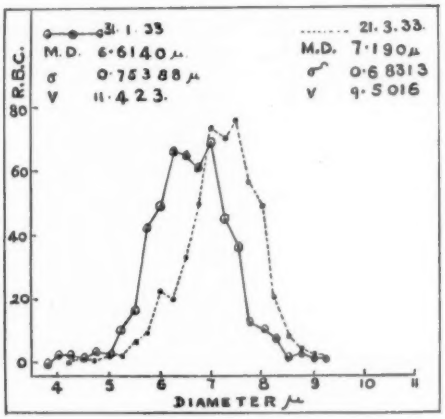
GRAPH 1.

Parsons and Hawksley. In all four cases the copper was administered according to Joseph's formula[1]. The effect on the mean diameter of the red cells, studied by the Price-Jones method in this case, was interesting. Before treatment with copper this was of microcytic type, and thus resembled other cases of nutritional anæmia, due to iron deficiency [11], after treatment the mean diameter was found to have returned

[1] 0·5% solution of copper sulphate, 1 c.c. per kgm. body-weight per day.

to normal (Graph 2). The mean diameter before treatment was 6·614 μ, and after treatment 7·1904 μ. These findings would agree with the acceptance of a similar mechanism in children, to that in rats described by Elvehjem and Schultze [4].

I have now had opportunity of investigating about eighty cases of nutritional anæmia, in all of which the diet was left unaltered and iron given, and where this failed to effect cure, copper added. Out of these cases four have required copper;



GRAPH 2.

three of these cases were studied under Professor Parsons, the fourth is here recorded, and illustrates that microcytosis occurs in copper deficiency anæmia and that the mean diameter returns to normal with copper therapy; it also illustrates the production of a reticulocyte response. It would seem that about one case in twenty can be shown by this method to be suffering from copper deficiency.

I am indebted to Dr. F. J. Poynton for allowing me to investigate and record his case. I would also thank Miss U. M. Bailey for her help.

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Section of Otology

President—W. J. HARRISON, M.B.

[*February* 2, 1934, *continued*]

DISCUSSION ON THE TREATMENT OF CHRONIC CATARRHAL OTITIS MEDIA (EXCLUDING OTOSCLEROSIS), AND OF DEAFNESS AND DRY SUPPURATIVE OTITIS MEDIA

Mr. W. M. Mollison: Chronic catarrhal otitis media is to my mind a gloomy phrase, and to diagnose this disease means a gloomy prognosis, a few kind words to the patient and advice about some kind of "aid." The treatment, therefore, to be effective, must be largely concerned with the beginning of the disease, though one may help the chronic cases that suddenly become worse owing to reinfections.

Dry suppurative otitis media is in itself a contradiction in terms, but I take it that this phrase means the condition remaining in the middle ear when suppuration has been brought to an end and the membrane, or what is left of it, shows scars or dry perforations.

Both the conditions, chronic catarrhal otitis media and dry suppurative otitis media are the results of previous subacute or acute inflammation in the middle-ear tract. In the first, perforation of the membrane has not occurred; in the second, perforation of the membrane has occurred and there has been suppuration, persisting for a shorter or longer time.

In the former cases the membrane is often nearly normal in appearance, though it may show opaque patches—so-called calcareous patches or radiating lines and it may be retracted and lacking the normal light reflex. When it is studied through the Siegle's speculum, movement may be defective or even absent, or may be obtained only over a small area (so-called "atrophic patches"). The eustachian tube may be obstructed or patent, as evidenced by the sound in the otoscope when inflation through the catheter is practised.

Just as acute suppurative otitis media leads to perforation of the membrane and later to dry perforations, so acute catarrhal otitis media leads to exudative otitis media, acute or subacute, and, if unrelieved, results in chronic catarrhal otitis media. It follows that early treatment of all ear infections is the only efficient method of treating subsequent deafness.

We have had the importance of perseverance in the treatment of acute suppurative otitis media drilled into us for many years. My earliest recollection of this was from Sir William Milligan; his ideal was that correct treatment of the "acute ear" should always result in normal hearing; and do away with the chronic suppurating ear and therefore of the deafness left when that suppuration ceased and left the dry suppurative otitis media. Mr. Charles Heath preached the same sermon and now, twenty years later, the lesson had borne fruit and we may flatter ourselves that there is less deafness as the result of acute middle-ear suppuration than formerly.

The non-suppurating cases are still a real difficulty. I think that from the standpoint of deafness, it is better to have a suppurating ear than a catarrhal one.

Acute catarrhal otitis media may affect the eustachian tube and the middle ear, the tube alone, or the middle ear alone—the tube escaping, or recovering from, the infection. If the catarrh is a mild one and in a child, attention is not drawn to it as there may be no pain, or pain so transient that it is disregarded, and certainly the deafness is not noticed. We, as aurists, know how even considerable degrees of deafness in children escape the notice of parents and teachers, and now with the use

of the audiometer in the examination of school children this knowledge is spreading to school officers. This discovery of deaf children will lead to treatment and doubtless to a diminution of chronic catarrhal otitis media. Once established in children a catarrhal otitis media leads to increasing deafness, compensated for in the young, but becoming worse with age. If the catarrh occurs in older children or in adults the fact is more readily appreciated and patients present themselves for treatment.

Treatment of tube and middle ear.—It has been stated that all catarrhal deafness is "moist," and it is tempting to accept this dictum and to incise every membrane so as to evacuate the mucus. Actually I have incised some membranes that appeared to be entirely normal in the hope of finding fluid but have been disappointed. Perhaps there had once been fluid but it had already disappeared.

It would appear that we have not advanced a great distance during the last sixty years in our knowledge of exudative otitis media. James Hinton, aural surgeon to Guy's Hospital, from 1863 till 1874 when he retired, in his "Questions of Aural Surgery," wrote of "accumulation of mucus in the tympanum."

"This result of the milder and more chronic forms of catarrhal inflammation of the tympanum comes before us in two forms, or rather stages; those, namely, of recent secretion and of old accumulation.

Every case of catarrh in which the secretion does not discharge itself through the membrane, or completely escape by the tube, presents the former condition. In how large a proportion of cases of the latter condition—that of old accumulation remaining after all inflammatory action has ceased—exists, and constitutes a main cause of impaired function, is a question for the future. My own little experience would tend to assign it a very important part."

and then of treatment :—

"Accordingly two methods have been proposed for the evacuation of the secretion: one, the incision of the membrane, revived recently by Schwartze; the other the introduction of a very thin elastic catheter through the eustachian tube completely into the tympanum, to withdraw the contained secretion by suction; suggested by Weber-Liel."

I should like to emphasize that the diagnosis of exudative otitis media is sometimes easy, sometimes very difficult. To see the hair-line of fluid through the membrane that moves with movements of the head, or small bubbles, is easy and gives the clue to the treatment, but there are cases in which no line is to be seen, in which the membrane is often substantially normal though sometimes lacking the normal sheen and typical normal appearance, though the history of the cases suggests fluid. Inflation with the catheter helps; in the first group the typical sound of fluid is easily heard, but in the second there is no "fluid sound"; instead, the sound is perfectly clear—in fact, too clear. I would go so far as to suggest that this too easily heard sound indicates exudation.

Diagnosis and treatment go hand in hand in these cases. Steps must be taken to remove the fluid. In the first place the Weber-Liel tube is passed through the catheter into the tympanum and suction applied—in the first or hair-line cases, fluid may be sucked out; this suction may need to be repeated two or three times before hearing is normal. In the second group, suction may reveal fluid and so establish the diagnosis. If the Weber-Liel tube does not succeed in this, incision of the membrane should be performed and the patient be made to perform Valsalva's self-inflation. In addition, drops of glyc. ac. carbol. may be prescribed, and small doses of potassium iodide internally.

It is in this second "hidden fluid" group that cases escape diagnosis and therefore treatment and pass on to chronic catarrhal otitis media. They certainly have escaped me.

Examples.—A patient complained of deafness in one ear, of three months' standing; he had been examined by two competent aurists who both gave a

hopeless prognosis, as they found a clear eustachian tube with normal membrane and the tests gave a response suggestive of otosclerosis. On listening through the otoscope the sound of inflation struck me as too clear, without any suggestion of "fluid sound." Nevertheless, by suction through a Weber-Liel tube a fluid was drawn out and the hearing returned to normal.

Recently a patient was seen who complained of deafness in the left ear, of three months' duration. The membrane was a little dull but moved with Siegle's speculum. The noise on inflation was very clear. Incision of the membrane and suction through a speculum produced a small amount of fluid, but when the patient "blew up" her ear a quantity of thick mucoid material filled the meatus and the hearing became normal. I have no doubt I have overlooked many such cases.

Does exudative otitis media ever pass to the antrum and mastoid cells as in suppurative cases? Four or five years ago there was under my care at Guy's Hospital a case that suggested this possibility. A child suffered from a clear mucoid discharge from the ear which persisted for weeks. Operation on the mastoid revealed similar clear mucoid discharge in all the cells and in the antrum; the discharge from the ear then ceased.

I do not know when an acute catarrhal otitis media becomes chronic. Physicians used to find some mystic significance in the period of three months: many of us will remember that an acute nephritis automatically became chronic nephritis at the end of that time! I do not think that aurists can fix arbitary time limits. How long can a catarrhal deafness persist before it refuses to be cured by inflation or other treatment? Recently a girl aged 10 was brought to me on account of deafness of three or four years' duration, with exacerbations whenever she had a cold. The throat had been operated upon twice and was clear: nasal and X-ray examination excluded sinus infection. The child could only hear spoken words at six inches from either ear and I feared permanent damage. However, politzerization was performed six or seven times and hearing was completely restored. I doubt if after four years' deafness such recovery in an adult could have resulted.

Here is another case that emphasizes this "time" difficulty. John R., aged 12, had been deaf for some months. He heard spoken words only at a few inches from either ear; he had been under treatment by an aural surgeon by inflation with only temporary improvement, for some months. He was found to have suppuration in both maxillary antra—a drainage operation was performed. Subsequently the eustachian catheter was used to inflate the tubes and it was six months before normal hearing was restored; I hope that this boy has been saved from chronic catarrhal otitis media.

The moral of such cases is that in children one need not despair of recovery of hearing even after long periods, and, that sources of infection must be removed both from the nasopharynx and sinuses.

Inflation of the tube in adults is not always easy and the passage of a bougie is often helpful. In passing, it is of interest to note that the bougie need not always be passed through the tubal isthmus but only up to the isthmus to allow of the subsequent passage of air to the middle ear. We all know of cases in which this manœuvre gives great relief of deafness in chronic catarrh. As well as the passage of a bougie other treatments of the tube have been advocated. Various fluids or gases may be blown through the catheter, e.g. 5% methyl salicylate in liquid paraffin; iodine in paraffin; or mercuric iodide gr. 2 in lanoline (R. Lake); chloroform vapour; hot air. Electric currents have been passed through metal bougies. Painting on a layer of flexible collodion helps temporarily flaccid membranes. Local treatment of the membrane may be attempted. Vibratory massage had its vogue. Making a permanent opening in the membrane has been successful in the hands of some. With the idea of softening adhesions in the middle ear, fibrolysin injections used to be given, but, personally, I never saw good results.

With the same idea, presumably, radium is applied to the mastoid, and in some

hands ionization is reputed to have been of considerable help. It is, however, difficult to dissociate the psychological effects of such treatments, from the physical.

Of the Zünd-Burguet method of treatment I have no experience.

Treatment of deafness in dry suppurative otitis media.—One must first remark on the excellent hearing of many patients with old dry perforations, some indeed hear approximately normally even with large perforations exposing the stapes. Most patients, however, with dry perforations suffer from a considerable degree of deafness; some are helped by an artificial drum of wool and lately celophane has been used and should be useful. Closure of perforations certainly helps, as Sir James Dundas-Grant has demonstrated. We must include also the use of various aids to hearing and lip-reading.

To sum up.—Unless we can treat effectively the early stages of catarrhal otitis by removing infective foci in the nasopharynx and accessory sinuses in addition to removing the exudate, we shall not have progressed further than did our predecessors of sixty years ago. By prompt treatment of suppuration in the middle ear we may hope to eliminate "dry suppurative otitis media."

Mr. C. P. Wilson: Treatment of any condition, unless purely empirical, must be founded on an appreciation of the pathology underlying the condition. Our ideas of the pathology of this disease are almost identical with those of the old masters of otology such as Politzer, and we have comfortably accepted their views because they seemed probable, and, with very little reason or critical research, we have assumed their theories to be proven facts.

We hear a great deal of the ultimate stages of catarrhal deafness; adhesions, atrophy of the membrana tympani and mucous membrane of the middle ear, and fibrosis of the submucous tissue of the eustachian tubes. Adhesive processes I have seen, but the only cases I have seen pathologically in which one expected to find these atrophic changes have all shown the presence of otosclerosis, and I have never yet seen a case which would agree with our orthodox views of the pathology of the late stages of the atrophic type of catarrhal deafness.

It is my opinion that cases of catarrhal deafness with atrophic changes of the membrana tympani and widely open fibrotic eustachian tubes have also the condition of otosclerosis. When a case has reached this stage I know of no treatment which can be satisfactorily shown to have improved the physical capability of hearing of a simple note, and, further, I think that any active local treatment is more likely than not to increase the rate of progress of the disease.

The treatment of patients in these late cases is purely educative and designed to improve their hearing from a social point of view—that is, their compensation of hearing. The social improvement in hearing as a result, for example, of electrical treatment can be amazing, as we have seen to-day, and I am enthusiastic about its value in the treatment of the disability which the deafness brings.

Now with regard to the treatment of earlier cases of catarrhal deafness: I would suggest first that the anatomy of the eustachian tube is a factor of more importance than we usually consider. The normal tube is a long narrow tube, but there is a small percentage of people who have a short relatively wide tube. This class of case with a short wide tube is more vulnerable to the spread of infection from the nasopharynx than the normal tube, but rarely becomes obstructed, and unless the infection is a virulent one, when an acute suppuration will probably supervene with extreme destruction of the drum, suppuration resulting from obstruction rarely occurs.

The ciliary action of the eustachian tube is sufficient to help the draining of the middle ear. People with eustachian tubes of this type have frequent attacks of a mild subacute catarrh with very little, if any, pain associated with the attacks because there is no distension of the middle ear, but the recurrent attacks of mild

inflammation leave them with one of two conditions: (1) An infiltration of the mucosal folds of the middle ear with later, fibrosis and contraction, resulting in indrawing of the membrana tympani; but still a patent eustachian tube. (2) The general onset and acceleration of an otosclerotic process with thinning of the membrana tympani and atrophy and degeneration of the mucosa of the middle ear.

Lately, it has been said that the deafness in these cases is due to thickening of the mucosa around the stapes, and this condition has been allied with otosclerosis and called peri-otic deafness. This again is a theory without pathological foundation, and I am not prepared to accept that these cases are not otosclerotic until I have seen a case which does not show otosclerotic changes pathologically.

The treatment in this class of case must never be local in the ear; manipulative treatment or catheterization cannot possibly be of use and will probably increase the fibrosis and the progress of deafness in those cases with an added otosclerotic element. Treatment is preventive and must be directed to the nasopharynx and pharynx.

I endorse everything which Mr. Mollison has said in this connexion. Adenoids and chronic infection of the maxillary antra are the most common causes of trouble. Correction of septal deformities is also important. Removal of tonsils, however, in the presence of a chronic infection in the nose, does, in my opinion, more harm than good. If the tonsils are removed and the sinus infection persists, there is always an increase of lymphoid tissue on the lateral wall of the pharynx and nasopharynx around the eustachian tubes. The nasal infection must be cleared up first, and conservative treatment of the tonsils may be part of the treatment for the nose; if the tonsils are so infected as to be incapable of recovery, then they may be removed later, but on no account should tonsils be removed until the nasal sepsis has been attacked.

Now what is to be done if such a case is seen with a moderate degree of already existing deafness? (and they are rarely seen in the early stages because the symptoms are so slight). The nose and nasopharynx must be tackled first, and then if eustachian catheterization shows the tube to be clear and widely open, local treatment to the ear must be stopped and any treatment of the deafness must be directed towards improving the compensation of hearing.

Catheterization in these people may apparently improve the hearing somewhat for the time being; this may be owing to the increased vascularity, stretching of adhesions, etc., but the hearing will quickly return to its previous level and the temporary gain may only be obtained at the expense of progressive diminution.

The only hope for these patients is to check the infective processes in the nasopharynx, damage the ear no further, and improve the compensation.

The patients with long narrow eustachian tubes have fewer attacks of infection from the nasopharynx, but the attacks that they do get are associated with eustachian obstruction, exudate in the middle ear and, possibly, suppuration. These are the people whose hearing is immediately restored during the settling down of an acute attack, by catheterization or politzerization and to whom Mr. Mollison has referred as the subjects of exudative catarrh. They are the subjects of catarrhal infection and eustachian obstruction, varying in severity from the mildly obstructed eustachian tube with discomfort and slight deafness, to the reddened drumhead, with some bulging and considerable pain; in these cases we may consider the advisability of paracentesis. It is this group to which the majority of cases belong and it is in these cases I think local treatment is of value.

It is when an acute attack is settling down, treatment is important in the later prevention of chronic deafness. In the acute stages the treatment is mostly nasal—i.e., inhalations of menthol and friars' balsam, sprays, etc., and in a majority of cases the acute condition clears up without leaving any obvious residual signs of the attack, except probably a mild degree of deafness unnoticed by the patient. It is when the attack becomes subacute, or if it is of a mild nature at the

beginning, with predominance of the obstructive symptoms, that the treatment is of importance.

The following is the routine treatment I adopt in these cases. Three times a day a solution of 10% argyrol containing ʒi glycerin to ʒi and a few drops of adrenalin, is dropped into the nostril with the head tilted towards the affected ear, and the drops are allowed to trickle towards the nasopharynx and collect around the eustachian tube. A few minutes later the nose is gently blown, to clear away any mucus and surplus drops, and a spray, such as a De Vilbiss with an olivary end, is then used to spray the nose with liquid paraffin containing a little menthol and chloretone. The nose is sprayed two or three times on each side and the patient swallows as the nose is sprayed with the object of opening up the eustachian tube. The opposite nostril is not closed, so that increase in pressure is so slight that there is no danger of mucus being blown into the tympanum, but as the tube is pulled open during the act of swallowing, a certain amount of oil will pass into the opening, stimulate the ciliary action, and help to prevent the closing of that section of the tube which has opened up.

As a rule this treatment will, after a few days, result in one spray eventually opening the tube throughout its length, and the hearing will then immediately be greatly improved. If this desired result does not occur after a week or ten days of the treatment, provided there are no acute symptoms present other than the deafness, the hearing is tested, and if there is any definite improvement in hearing, the patient is instructed to carry on with the same treatment until such time as there is no longer any improvement yet the hearing has not returned to normal. When this stationary point has been reached, catheterization is performed and the treatment continued. Sometimes the hearing improves after the catheterization, only to deteriorate again within a few hours or days; in such a case the catheterization must be repeated at intervals care being taken that the blowing of air into the tympanum is done gently and without force, and it is done until the hearing returns to normal or until improvement no longer results.

If a stationary point is reached and the hearing is not normal, then it is probable that it was not normal before the attack and that the best level of hearing in that patient has been reached. After catheterization, I, personally, blow along the catheter a solution of argyrol or chloretone inhalant.

I believe that otosclerosis is a much more common complication of catarrhal deafness than is generally realized, and if it is at all comparable with other diseases it will be influenced in its progress by repeated infection and by trauma. Repeated infection is most common in the short wide tube group, and these are the cases with the late atrophic changes that I have mentioned. In the long narrow group too, however, there is also the possibility that repeated trauma in the shape of recurrent forcible eustachian catheterization may predispose to the onset and progress of the complication, and catheterization should be undertaken only when there is definite eustachian obstruction and only continued if it results in definite improvement of hearing. For the treatment of these cases, inflation by Valsalva's method or politzerization, is in my opinion, unsound, unscientific, and unsafe.

After repeated attacks, which are neglected in that the hearing has not returned completely to normal, cases in this group may show chronic indrawing of the membrana tympani and have limitation in the movements of the ossicular joints. When this stage has been reached, eustachian catheterization is the only treatment of value. It should be combined, I think, with oto-massage, the most important point in the massage being to make sure that the first stroke is a stroke of suction and not a stroke of compression, but once again I would like to emphasize the point that this treatment should only be continued if improvement in hearing results.

With regard to catheterization in these cases which, when first seen, already show existing chronic changes, there is one small point to which I will draw attention. In treating some of these cases which seemed to have marked eustachian obstruction, one occasionally obtained perfectly free entry at one catheterization but without any more improvement in hearing than at other times when no air entry was obtained. I made a practice of passing a nasopharyngoscope in these cases and discovered that the cause of failure to catheterize successfully was the anatomical shape of the floor of the nose, which was convex from before backwards and made it impossible to turn the point of the catheter outwards into the orifice of the tube, the beak of the catheter always passing above the tube, however much the tip of the nose was tilted upwards.

I found that if the catheter was bent 1 inch from the beak slightly downwards at right angles to its usual curve, the beak then lay at a lower plane than usual and passed into the tube quite easily. I think this is worth bearing in mind when a eustachian tube presents difficulty in catheterization.

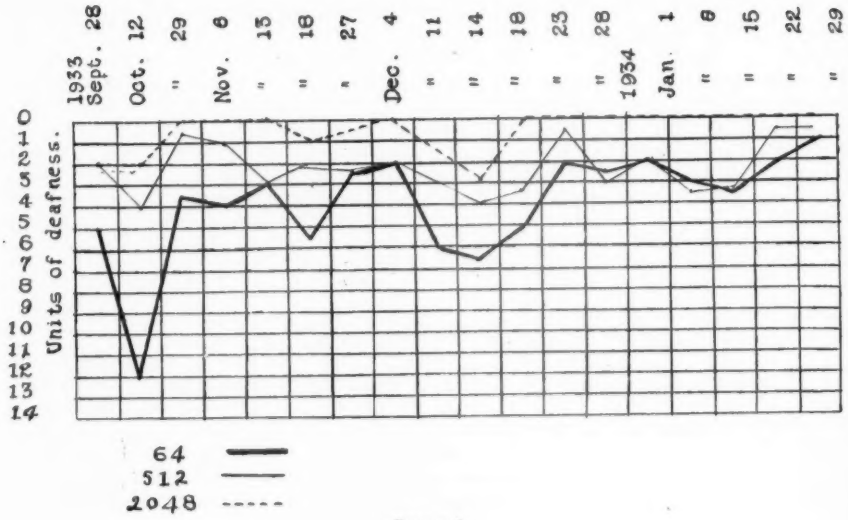
Dr. Albert A. Gray: The pathological changes which are found in the middle ear in the conditions under discussion are represented in the photographs now shown on the screen. The first shows a fairly early stage of the adhesions which may occur after an acute or subacute middle-ear inflammation which has not gone to the stage of suppuration. In these cases the adhesions may be found in various regions of the middle ear, but are perhaps most common about the head of the malleus and body of the incus.

The second photograph shows the adhesions which may be found after the drying up of a chronic middle-ear suppuration. Not infrequently these adhesions bind down the remains of the tympanic membrane to the promontory. Both of these conditions are the result of inflammation either acute or chronic.

But there is another condition in which newly formed fibrous tissue may be found in the middle ear without any preceding inflammation or exudation, and I cannot help thinking that many of these cases have given rise to the legend of "dry catarrh of the middle ear," or "adhesive processes in the middle ear." The change consists of a very slow increase of the connective tissue in the muco-periosteum of the middle ear. It is found in the region of the footplate of the stapes. It is not inflammatory in character. There is no round-cell infiltration and the epithelial covering is not broken, and there is no dilatation of the blood-vessels. It is in fact a degenerative process, and so far as my investigations go, it never occurs except in association with otosclerosis. An interesting feature of these cases is the fact that this newly formed connective tissue sometimes absorbs the newly formed otosclerotic bone with which it lies in contact.

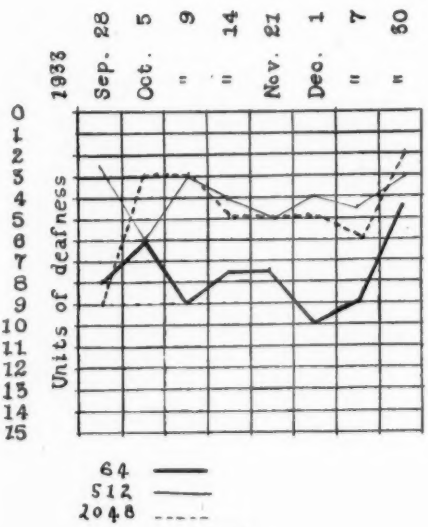
Now, as Mr. Wilson has pointed out, inflation could not possibly benefit these cases, because they are in reality cases of otosclerosis in which bony ankylosis at the stapedio-vestibular articulation either has already occurred or will occur. Inflation can do no good and very probably will do harm.

Mr. A. Lowndes Yates showed graphs illustrating a new method, known as the progress graph, which he had introduced for the purpose of recording improvement or deterioration in the hearing. The number of units of deafness for air conduction for notes of 64, 512, and 2048 double vibrations per second were recorded before treatment each time the patient came. It was thus possible to determine the degree of the improvement and to alter the treatment if it were found that this was not effecting the desired results. Graph 1 showed a case which illustrated the method. Graph 2 was shown because the patient had made no improvement in actual hearing as a result of treatment but was quite confident that his hearing had improved. This graph was shown to demonstrate how easy it was to form the

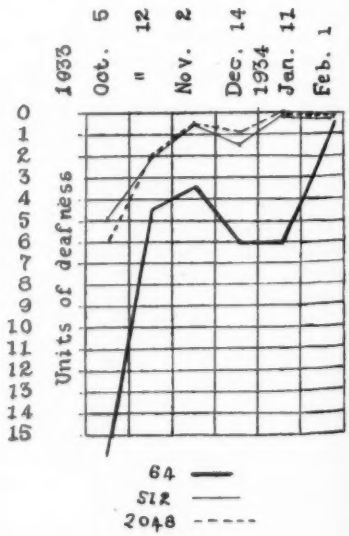


GRAPH 1.

The numbers of units of deafness indicate the number of times the intensity of a sound audible to the normal ear has to be doubled before the patient hears it.



GRAPH 2.



GRAPH 3.

opinion that the treatment had effected an improvement if one relied only on the statement of the patient and did not use some form of quantitative test. Graph 3 was a record of the hearing of a patient who, when he first came for treatment, had a history of increasing difficulty in hearing for fifteen months. There were 5 units

of deafness for bone-conducted sounds for a note of 1024, and 2 units for a note of 512. This deafness for bone-conducted sounds was not shown upon the graph, which gave the air conduction. It will be seen that the hearing returned to normal and it may be stated that bone-conducted sounds were also heard quite normally at the end of treatment.

These cases were treated by a method which he thought had proved of use. In the earlier cases which had been treated eustachian aspiration by catheter had been practised. He had found, however, that this occupied much time, and in the three cases which were recorded in the progress graphs the aspiration of the eustachian tubes had been accomplished by a method very similar to that of Proetz, in which 3 c.c. of liquid paraffin was introduced into the nasopharynx, the patient lying on his back, and a negative pressure then induced within the nose. If when the patient came for treatment it was found that the treatment at the last attendance had not improved the hearing, the inflammatory condition of the sinuses was also dealt with by a modified method of displacement. This seemed to give good results and he now only employed the tympanic catheter in those cases in which no benefit had resulted from this simpler form of aspiration. Mr. Wilson had referred in his opening paper to the injection of argyrol into the eustachian tube, and the speaker asked what effect that had upon the cilia. He (Mr. Yates) thought from the experimental evidence he had collected that it tended to cause ciliary palsy.

Mr. Thacker Neville said that in the case of chronic catarrhal deafness anything which dilated the blood-vessels of the inner ear seemed to help. Recently rheumatic specialists had been using histamine for rheumatism, and one patient who was having this treatment said that her hearing was much improved. Histamine, however, caused redness and œdema of the skin, and headaches. The other treatment was diathermy, and this he used as a routine in all cases of catarrhal deafness. By it one applied heat to the ears for twenty minutes. He also used the diathermy cautery to coagulate the inferior border of hypertrophied inferior turbinates, having first excluded the presence of a sinusitis. This procedure could be carried under gas-and-oxygen anæthesia and it improved the hearing.

He had tried ionization but the ions used had to be introduced from the negative pole. Though patients did not object to the positive pole used with zinc in otitis media, they found the introduction of ions from the negative pole unpleasant.

A treatment, which was much neglected in England for this condition, was spa treatment. The French had treated these cases with sulphur vapours insufflated through a catheter, besides ordering sulphur waters to be drunk. The sulphur which is excreted through the respiratory tract is anti-catarrhal. In France, children, after removal of adenoids, underwent a course of sulphur water for this affection.

Dr. A. R. Friel: Eustachian obstruction and catarrhal otitis media in children are usually accompanied or preceded by rhinitis. Any treatment which is effective for the rhinitis is a preventive or curative agent for the ear condition. Such a treatment is that devised and perfected by Dr. Gautier of Paris and called diastolization.

Acute rhinitis may readily become chronic owing to retention of infected mucopurulent secretion in the posterior part of the floor of the nose. It is retained there owing to the inability of the child to blow his nose on account of the swelling of the inferior turbinal. When this swelling is reduced the passage is open, the secretion can be expelled, and the patient quickly recovers. Moreover the irritation of adenoid tissue in the nasopharynx by this discharge is also removed and the swelling due to the irritation subsides.

Diastolization consists in the introduction of soft rubber hollow bougies along the floor of the nose into the space between the inferior turbinal and the septum. The

mild stimulus causes, by reflex action, contracture of the blood-vessels in the turbinal so that the latter shrinks and the passage becomes open. This treatment is of economic importance, because the condition for which it is of use is very common. It is easily carried out, is usually painless and is effective for this congestive condition.

As the nose and nasopharynx recover, the eustachian congestion subsides. If this is of some duration, vibration with a wire, inside the bougie and attached to an iron rod placed between the poles of an electromagnet which is energized by an alternating current hastens recovery. The vibration should not be kept up for long without making a pause as the reflex would be worn out.

I have also found a weak solution of nitrate of silver applied by Yankauer's applicators of use. These are easily made by taking fifteen inches of fine stainless steel wire doubling it and twisting it with a rotating apparatus such as a lathe or hand drill. An inch of the closed end is wrapped with a little cotton-wool, passed through a eustachian catheter, dipped in a weak solution of cocaine or percaine, and passed into the tube. It is left there for a few minutes and the process repeated with nitrate of silver which is left in position for three or four minutes.

To restore the position of the drum membrane as well as to open the eustachian tube, politzerization is employed. The results of treatment are checked by the audiometer.

The best way to prevent the results of chronic catarrhal otitis media in adults is to treat the children.

Mr. T. B. Layton said that the part of the body concerned in this discussion was one in which it was difficult to work out the pathological anatomy. For many years changes in the middle ear had been assumed to be the physical basis of the deafness in cases such as were being considered that day, and changes in the osseous tissue around the labyrinth had been demonstrated in these other cases that were called otosclerosis. There was a third possibility, namely that changes in and around the mastoid antrum afforded the physical basis of deafness in one or both of these groups.

The mastoid antrum was not usually considered to be a part of the organ of hearing, and so far as he knew no physiologist had considered it in relation to any theory of this special sense, but he felt that it must have something to do with it. There were two things that made him think this: one anatomical, the other a clinical observation.

It was with him an article of faith that structure was the basis of all function. The mastoid process was a part of the musculo-articular system of the body, an excrescence of bone for the better attachment of the sternomastoid muscle analogous to the lesser trochanter with the ilio-psoas. Into this mastoid process there extended the middle-ear cleft, and if the middle-ear cleft was a part of the organ of hearing, the furthest end of the diverticulum must have something to do with this function.

The clinical observation he owed, in the first place, to Mr. Mollison, and he was the more impressed by it because for long he had refused to believe it. A person suffering from otitis media was not usually deaf, but if he were so it was certain that the inflammation had extended into and involved the tissues of the mastoid region. This had been definitely proven by clinical observation on the operating table and by radiography; and it would seem that the deafness was more noticeable when the mucous membrane was swollen than when actual suppuration had taken place. If then obliteration of the cavity caused deafness it was clear that the cavity had some rôle in the function of hearing.

He suggested that changes might also occur in catarrhal inflammations, and that in the case of the child—in which there was evidence of a free entry of air

into the middle ear—the fluid sucked out by Mr. Mollison came across that cavity from the mastoid antrum and its associated cells. He further suggested that the reason why such cases did not recover in the adult was that sclerosis of bone around the antrum had already occurred and was a factor in the deterioration of hearing, whereas in children sclerosis of the bone in this region had not yet happened.

This line of thought was to him a new one but it was based upon the two definite facts, and indicated a line along which investigations might be made, and such investigations should be possible, as they could be based upon clinical observations and radiography.

Mr. Eric Watson-Williams said that one point was worthy of emphasis, namely, how very little the appearance and condition of the tympanic membrane was correlated with the degree of deafness. One saw a patient fairly deaf (not otosclerotic) but with little change in the tympanic membrane. One also saw patients who showed big distortions of membrane with distortion, scars and perforations, but whose hearing was apparently unaffected. The condition of the tympanic membrane was as often misleading as it was helpful in giving a clue as to the cause of the deafness.

Mr. Wilson had mentioned a class of case having short eustachian tubes: he (the speaker) would like more detail about this. Obviously the eustachian tube reached the middle ear; did Mr. Wilson mean that the eustachian cushion was further back in the nasopharynx than normal?

He had been disappointed in not hearing more about the medicinal treatment of these patients. There was a definite group in which the trouble seemed to be a degenerative process affecting the mucous membranes of nose, pharynx, and ear (he was not referring to the mucosal degeneration of otosclerosis). These patients appeared to be suffering from iodine deficiency, and he had obtained a certain amount of success by treating them with thyroid gland substance.

Mr. Harold Kisch said he supposed that most members of the Section had been faced with the problem whether or not to perform submucous resection or other operation for nasal obstruction so as to help cases of chronic deafness. He had a test which he regarded as of some use. If one tested the hearing of a patient before carrying out any manipulation, and then sprayed the nose with a solution of cocaine and adrenalin, in a certain number of the cases the hearing could be demonstrated to have improved, and in these he had found that operation for the nasal obstruction was helpful.

Mr. J. F. O'Malley said he thought the ground had already been extensively explored in this discussion, but speakers seemed to have gone over the views which had been prevalent for many years, though the two openers presented them in a fresh garb. What seemed necessary in order to improve the position of otologists in regard to treatment was to gain a better understanding of the physiology of the air-movement influences in the middle-ear cavity, which was essentially an air cavity, with variations of pressure from time to time. All the methods, such as inflation and aspiration, offering prospects of benefit, seemed to be concerned with altering the air pressure in the middle ear. Mr. Layton approached this conception when he spoke of the whole middle-ear cleft, as there was a passage of air all through the eustachian tube and into the mastoid antrum, and if the maintenance of air contents of these cavities was efficient and capable of varying, hearing seemed to be satisfactory. Conditions which altered these seemed to be conditions which deteriorated the functions of the ear.

Mr. Gilroy Glass asked if the fluid in the middle ear in catarrhal otitis media might not be the cause of a certain number of the cases in which a mastoid wound refused to heal. He had recently had a patient with such a condition, who by blowing his nose could expel fluid from the post-aural sinus. It would appear in this case, to be a sequel of purulent otitis media.

With regard to treatment by diathermy, he had, recently, in collaboration with Mr. A. Tweedie, tried this in about thirty cases. A few reported improvement in hearing, but accurate testing did not confirm this report ; indeed in some cases it revealed a deterioration.

Mr. H. V. Forster said that the late Sir William Milligan had suggested that deafness in the so-called chronic catarrhal types of otitis media might be explained by thickening about the round window, but since then Hughson and Crowe, following Weaver and Bray, had shown how the intensity of transmitted sounds of certain frequencies appeared to be increased in the cat after loading the round window.[1]

He was interested in Mr. Mollison's remarks about the more easily heard inflation sounds in cases of tympanic exudate and noticed that the Weber-Liel catheter passed easily up the eustachian tube. He did not believe that the catarrhal exudate was a vacuum exudate in the average case. Fairly strong suction was needed to draw off exudate through the Weber-Liel catheter. He used the stiff bulb of Siegle's speculum.

With regard to what Mr. Watson-Williams had said, he was first impressed after the routine examination of the drumheads of school children when, in so many cases of affected tympanic membranes, deafness had not been noticed.

Mr. Wilson (in reply) said he did not think that argyrol had any detrimental effect on the ciliæ. He said this partly on clinical observation, but mostly considering its effect in infected antra. If argyrol was instilled after puncture, as a rule, cases in which it returned very slowly did not get better, and required to be drained. The cases in which the argyrol returned quickly, recovered without operation so that the argyrol had not had any marked ill-effect on the ciliæ.

He had not mentioned suction because Mr. Mollison had already referred to it. He thought suction before inflation should be practised, particularly when catheterizing the patient for the first time. Inflation should be practised after suction.

Mr. Layton had referred to the importance of the pathology of the disease, and that was what he (the speaker) tried to stress. He and his colleagues of the Ferens Institute had tried to perfect the cutting of temporal bone sections, but they could not get enough suitable cases. He hoped members of the Section would send bones from cases the clinical history of which was known to them.

In answer to Mr. Watson-Williams, the shortness of the eustachian tube was possibly a developmental defect, possibly an anatomical variation. In childhood the tube was wider and shorter and more horizontal than in the adult. Heads also varied in shape, but when one saw a long head it did not necessarily follow that this was associated with a long and narrow eustachian tube. In such a case the length of the nose from the anterior to the posterior nares was greater than would be thought, judging by the length of the head, and the eustachian tube might still be short and wide.

[1] Hughson, Walter, and Crowe, S. J. (Baltimore), "Experimental investigation of the physiology of the ear," *Acta Oto-Laryngol.*, xviii, Fasc. 3.

Section of Tropical Diseases and Parasitology

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The Classification of Snakes in accordance with their Dentition and the Evolution of the Poison Fang

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THE title of this paper is not strictly accurate. The classification of snakes depends upon many more details of structure than their dentition, and it is with one particular group only that we are now concerned.

Snakes have been derived from lizards or some lizard-like creature, and most of the primitive snakes still show some evidence of their four-footed ancestry, generally by the presence of a pelvis and even vestiges of hind-limbs. From one of these primitive groups the family which is called the *Colubridæ* was formed, and it is from them that the poisonous snakes have been derived.

The *Colubridæ* are a very large family. They constitute the vast majority of the species which are living now. They can be divided into three series according to their types of teeth, namely the *Aglypha*, which have solid teeth, without grooves upon any of them; the *Opisthoglypha*, which have grooved teeth or fangs at the back of the mouth: and the *Proteroglypha*, which have tubular or canalized fangs in the front of the mouth. The last series includes, generally speaking, all the venomous snakes. As a group they stand out clearly by themselves, while the dividing line between the *Aglypha* and the *Opisthoglypha* is not so clearly drawn.

These three series do not, except in a very fragmentary way, depict the family tree, but they serve two excellent purposes. First of all they are a tremendous help in identification. To be able, after a few moments examination of the teeth, to place a snake in one of the three groups limits the field of search considerably. And, from the medical point of view, there are occasions when it is very useful to be able to say whether a snake is poisonous or not. Secondly, the grouping of the *Colubridae* into three series does represent the general trend of evolution. The *Opisthoglypha* have been derived from the *Aglypha*, and both have, in their turn, given rise to the *Proteroglypha*.

The venomous snakes, therefore, are comparatively late arrivals upon the earth, and in their own particular way they represent a high degree of specialization. And step by step with the evolution of the poison fang has been the evolution of the salivary gland. From an evolutionary point of view the fang is secondary to the gland; it is merely the instrument for the conveyance of the poison.

Series I.—The *Aglypha*: Snakes with solid teeth, without grooves or perforations. Their bite, in so far as any venom is concerned, is not dangerous or harmful in any way. It has been recorded within the last few years, that the saliva of some of them is toxic for small vertebrates such as frogs and fish, but the observations are confined to laboratory experiments and need confirmation. Possibly it is some form of anaphylaxis and not a true venom.

Series II.—The *Opisthoglypha*: Snakes with grooved teeth at the back of the maxillary bone. These teeth, generally two in number, but sometimes three or four, are usually larger than the others. The groove is situated on the antero-external face of the tooth except in rare cases where it is quite external. The bite from these snakes is often toxic to the creatures they feed upon, but only in rare cases is it dangerous to man.

They are sometimes called the back-fanged or semi-poisonous snakes, and the idea has grown in the last few years, not only among popular writers but among some zoologists, that many species in this group are dangerous to man, although their bite may not be fatal.

This, I believe, is not the case. As far as man is concerned, the vast majority of them are quite harmless.

Series III.—The *Proteroglypha* :—Snakes with the fangs at the anterior end of the maxillary bone and therefore in the front of the mouth. The grooved tooth has been converted into a tube or canal for the greater part of its length. Most of the snakes in this series secrete a venom which is highly toxic to man.

The *Proteroglypha* can again be divided into two distinct groups and these represent definite lines of evolution. All the snakes that we call the vipers have travelled along one line, all the rest, known as the Elapine Snakes, have travelled along another.

The difference between them is this: In the *Elapidæ* the poison fangs are comparatively short and the maxillary bone long, and it bears upon it behind the fangs a varying number of smaller teeth, from one to eighteen. These smaller teeth are usually grooved but are never tubular. In many of the *Elapidæ* also, the teeth upon the palatine and dentary bones are more or less distinctly grooved.

In the vipers the maxillary bone is very short and bears the fangs only. It is movably attached to the pre-frontal and the ectopterygoid, so that, when the creature wishes to strike, the bone and the fang upon it can be erected. This is quite different from the Elapine fang and its mode of origin must have been different. The normal position of the Elapine fang is more or less at right angles to the maxillary bone and its position in the mouth is almost vertical. The normal position, by which I mean the resting position of the viperine fang, is almost horizontal in the mouth. This resting position, the ability to fold the fangs back in the mouth, has, in fact, become imperative for the preservation of the species. In most of the vipers the fangs are now so enormous that they were fixed in the erect position, the creature would be unable to close its mouth.

The tubular fang of the *Proteroglypha* has been formed from the grooved tooth, or one with open canal, by the growth forwards and inwards of the margins of the groove, until finally the two meet and form a canal. In the *Elapidæ* and often also in the *Viperidæ*, the line of union can be seen, but the canal itself is closed for the greater part of its length.

In snakes there is a perpetual succession of teeth, the old ones being pushed out by the new teeth that grow up to replace them.

In the *Viperidæ* it is usual to find, on the inner and hinder side of the poison fang, a cluster of three or four or more reserve or successional teeth, in varying stages of development, waiting to take their turn. In the *Elapidæ* only one or two can be seen with the naked eye.

There is no direct connection between the poison duct and the poison fang. The duct, when it reaches the fang opens into, or becomes expanded into, a small cavity in the muscular folds which surround the base of the tooth and overlies the opening in the canal. Consequently the loss of a tooth does not cause any injury to the duct and no repair is needed. The supply of venom is always ready for the next tooth which is almost in position before the old one is shed.

Evolution of the poison fang.—Of the evolution of the poison fang in the Elapine group of snakes we know nothing. The initial stages which led up to the formation of that type of fang—that is to say, a fang placed at the anterior end of the maxillary bone, and having other teeth behind it—has not yet been found. No non-venomous snake with grooves upon its anterior teeth is yet known. But it seems evident, from the character of the maxillary bone, that they have been evolved from the *Aglypha* and not the *Opisthoglypha*.

The evolution of the viperine fang is clearer. Most of the stages which led up to it can be seen in snakes living to-day, and one can form a very sound theory as to how it arose. The vipers have been derived from the Opisthoglyphous snakes by the gradual movement forward and shortening of the maxillary bone. As it became shorter the teeth on its anterior part were lost and finally a stage was reached when only the posterior fangs remained. These would then be at the front of the mouth. One can arrange among the *Opisthoglypha* a complete series showing this gradual shortening of the maxillary bone, starting from *Oxybelis* which has twenty or more teeth in front of the fangs and culminating in *Miodon*, which has only two. The ability to erect and depress the fangs became developed as the maxillary bone grew shorter, and *Xenodon*, one of the Aglyphous snakes, actually has the power to move its maxillary bone in just the same way as the vipers can.

Xenodon is the only snake we know of that has the true viperine type of movement, but the power to erect in some degree the maxillary bone is widely spread among the *Proteroglypha*. It is, in fact, only a further development of the power to move the jaw-bones independently, which all snakes possess.

Snake Bite: its Mechanism and Modern Treatment

By N. Hamilton Fairley, M.D., F.R.C.P.

Snake bite continues to be a problem of interest in tropical countries, and though nowhere a really serious menace to life, many cases occur, especially in India, Brazil and the United States. From both the latter countries recent reports indicate a marked lowering of the death-rate following the general use of specific polyvalent antivenenes, but though a bivalent antivenene for cobra and Russell's viper is manufactured in India, where the official mortality-rate approaches 20,000 per annum, its use is by no means widespread, especially amongst the populations of the jungle villages.

Both non-poisonous and poisonous snakes are carnivorous and the difference between them lies mainly in the absence of deeply grooved or canalized fangs for efficient inoculation purposes. Non-poisonous snakes such as the *Boïdæ* and aglyphous *Colubridæ* sometimes bite man, and occasionally local sepsis or, even septicæmia, may ensue owing to a secondary bacterial infection. In the back-fanged colubrids (*Opisthoglyphæ*) a poison gland has developed, yet, with the exception of the boomslang, they are not poisonous to man, since they cannot effectively inoculate their venom owing to the posterior position of their fangs. The poisonous sea-snakes (*Hydrophinæ*) possess very potent venom, but despite this and the fact that their fangs are anteriorly situated, they are fortunately handicapped as far as man is concerned by their small heads, poor gape and relatively inefficient bite.

The ophidian poison gland has long been recognized as the homologue of the mammalian parotid. Histologically it is a serous gland of compound racemose type consisting of an interalveolar frame-work of connective tissue and of alveoli lined with short columnar epithelium in whose capacious lumina the venomous secretion is stored. The gland, itself, is situated above the upper lip behind the orbit, and in the proteroglyphous *Colubridæ* the laterally compressed venom duct passes forward in its course along the upper lip margin to open by a papilla on the anterior wall of the vagina dentis at the base of the grooved fang; during its course supralabial mucous glands may also pour their secretions into the duct.

Phisalix [1] in her classical work on the ophidia, has emphasized the anatomical and functional independence of the pterygo-palatine-transverse arches in the non-poisonous constricting snakes, as well as in the colubrids and the vipers, and has shown a gradual series of transitions commencing with the *Boidæ*, passing through the aglyphous, opisthoglyphous and proteroglyphous *Colubridæ* and attaining their highest evolutionary development in the *Viperidæ*. These changes include

shortening of the skull and of the superior maxilla, and elongation of the quadrate bones. Fairley [2], in a study of the dentition and biting mechanism of the common Australian snakes, employed the maxillary index which was obtained by dividing the length of the skull, as measured in millimetres from the anterior border of the premaxilla to the posterior border of the occiput, by the length of the superior maxilla; this afforded an accurate basis for comparison of the maxillary shortening in different species of ophidia, and a definite relationship was traceable between maxillary shortening and decreasing maxillary teeth on the one hand, and the forward projection of the pterygo-palatine-transverse arch on the other. A similar index, the quadrate index, was introduced for the quadrate bone, lengthening of which permits greater depression of the mandibles. For all seven snakes studied, the maxillary and quadrate indices were found to be inversely related throughout the series, i.e. relative to the length of the crania the quadrate lengthened as the maxilla shortened in the different species. A steady transition was noted, the narrow-headed brown snake with its low maxillary (2·6) and high quadrate (3·45) index approximating to the non-poisonous species, whereas the broad-headed death adder with its high maxillary (3·7) and low quadrate index (2·0) approached the vipers. The other colubrids held intermediate positions.

The Mechanism of the Bite.

There are four distinct phases when a poisonous snake bites: (1) The strike; (2) opening of the mouth and elevation of the fangs; (3) closing of the jaws and the injection of venom; (4) retraction of the fangs.

(1) *The strike.*—In this phase the snake throws itself forward with great rapidity and violence, the distance covered not generally exceeding one-third of its length. The vipers strike with greater velocity than the colubrids, some of which—especially the hooded species—raise the head from the ground, so compensating to some extent for the limited mobility of the fangs.

(2) *Opening of the mouth and elevation of the fangs.*—Most poisonous snakes commence the strike with closed jaws, but as the head approaches the victim the mandibles are depressed by a rapid contraction of the digastric, cervico-mandibular and vertebro-mandibular muscles and simultaneously the fangs are elevated or rotated forward by the forward swing of the pterygo-palatine-transverse arch produced by the contraction of the spheno- and parieto-pterygoid muscles.

The fangs of the *Colubridæ* are invariably grooved and are generally shorter than those of the viper, and their capacity for forward rotation is much more limited. My own studies on the Australian colubrids revealed a wide range of variation in the mobility of the fangs, the degree of elevation from extreme retraction to maximal protraction varying from 10°-15° to 45°-50° in different species. Each pterygo-palatine-transverse arch acts as a single entity, and when the protractor muscles of the palate draw the endo-pterygoid forward, they invariably bring with it the palatine bone and the ecto-pterygoid which impinges on the posterior arm of the maxilla, driving the maxilla forwards and upwards on the articulating surface of the prefrontal. This produces a variable degree of elevation and forward rotation of the fangs,[1] which are ankylosed to the inferior surface of the maxilla; its extent can be judged by the angle formed at the ecto-pterygoid maxillary junction which, in the resting position, forms a straight line. In these snakes the smaller the maxilla (i.e. the greater the maxillary index), the greater the forward movement of the pterygo-palatine-transverse arch and the greater the degree of forward projection of the fangs. This mechanism differs from that of the vipers in which the movement

[1] Should this movement be doubted it can readily be demonstrated by pithing the snake, dissecting up the palatal mucous membrane and electrically stimulating the protractor and retractor muscles acting on the palatine arch; alternatively, skulls can be prepared with the palatine arch in different positions.

of the maxilla on the prefrontal is a true rotary one and not a forward and upward sliding movement as described above.

(3) *Closure of the mouth and the injection of venom.*—Closure of the jaws follows, a result brought about by the simultaneous contraction of the anterior, middle and posterior temporal muscles which strongly elevate the mandibles. In the colubrids the venom gland is also compressed by the superior and inferior portions of the anterior temporal muscles, producing torsion on its capsule with the expulsion of venom from the gland along the duct, the papilla of which becomes approximated to the groove at the base of the fang. Fixation of the jaw is important in effective biting by colubrids, as emphasized by Acton and Knowles [3], but in certain Australian species venom may sometimes be observed to spurt a considerable distance during a snap bite at a time when no object is actually being bitten.

In the vipers there is an entirely different anatomical arrangement of muscles acting on the venom gland; expulsion of its contents is instantaneous and independent of fixation of the lower jaw.

(4) *Retraction of the fangs.*—Immediately following the insertion of the fangs, and actually accompanying the discharge of venom, contraction of the retractor muscles (the parieto and spheno-palatine and the internal and external pterygoid) which operate on the pterygo-palatine-transverse arch occurs, dragging the elevated fangs downwards and backwards through the tissues.

Though the four stages including the inoculation of venom are described separately, they occur in nature as a series of rapidly co-ordinated movements, several lethal doses being injected in a fraction of a second in some instances—especially with the vipers.

Dental impressions of the bite.—Following the bite of a non-poisonous snake numerous punctures may be observed on the skin, and if a dental impression be made on Kerr's impression compound of one of the constricting snakes such as *Python spilotes*, one finds five different groups of teeth represented, viz., the pre-maxillary, two lateral rows of maxillary teeth and two more centrally placed rows comprising the pterygo-palatine teeth.

In the elapine colubrids and vipers impressions of the bite in dental wax generally show the two lateral fang punctures with complete absence of post-maxillary teeth markings accompanied by two inner rows of pterygo-palatine indentations. Sometimes, however, only one fang-mark may be noted, owing to the absence of a functional fang on the other side, while in other cases three, or even four, fang-marks may be observed, due to the forward position sometimes assumed by the reserve fangs. In certain colubrids a limited number of post-maxillary teeth punctures may be encountered, their number being governed by the length of the maxilla. The only teeth-marks at all commonly encountered on human skin, however, are those attributable to the fangs; they may be indicated by two small petechial punctures which, in the vipers, ooze blood. In tiger snakes, death adders and copper-heads Fairley and Splatt [4] found that the distance between the fang punctures afforded a fair index to the venom yield; inter-fang measurements should thus have clinical significance in indicating the dosage of venom likely to be injected and the probable amount of antivenene required. Fatal results, however, may follow inoculations from a single fang, while in colubrid bites it is well to remember that the fang marks are by no means always demonstrable.

Venom Yield and the Certainly Lethal Dose.

Apart from the efficacy of the inoculation apparatus, the yield of venom and its certainly lethal dose must be considered in assessing the potential lethality of any given species of snake for man; these factors must also be taken into account when determining the dosage of specific antivenene likely to be effective.

The question of venom yield is an important one. In the first place it is not universally appreciated that within limits a snake controls the amount of venom inoculated, and that a deadly colubrid may bite on several occasions within a few minutes, and each time injects several lethal doses; subsequent milking may reveal considerable quantities of residual venom in the venom gland.

Factors such as captivity, disease, and starvation may affect the venom yield adversely, and recent feeding may temporarily reduce the content of the venom gland. These considerations are matters of importance for they serve to explain why a deadly snake does not always kill. In addition, such factors as the intervention of clothing, strong daylight (in the case of nocturnal snakes), and diminished vision during ecdysis, may modify the strike.

The certainly lethal dose of venom varies within wide limits when tested on different animal species, and in experimental studies it appears advisable to work either with monkeys or with animals like sheep or goats, which approximate to the body-weight of man. The killing capacity of different venoms for sheep, estimated in terms of the average venom yield, was found by Fairley [5] to be as follows: 118·0 for the tiger snake (*Notechis scutatus*), 31·7 for the cobra (*Naia tripudians*), 2·2 for the Russell's viper (*Viper russelli*), 84·7 for the death adder (*Ancanthopis antarcticus*), 8·9 for the copper-head (*Denisonia superba*) and 1·5 for the black snake (*Pseudechis porphyriacus*). These figures only represent the number of certainly lethal sheep doses in the average yields and not in the maximal yields which were very much higher; they serve to illustrate the colossal potential killing power of certain colubrids for animals of a body-weight approximating to that of man.

Treatment of Snake Bite.

The essential clinical problem in snake bite revolves round the question whether a lethal dose of venom has been injected into the tissues in the first instance, and, secondly, whether a lethal dose has been absorbed into the circulation by the time the patient has been seen by a medical man. Under the latter conditions specific antivenene alone is able to save life.

Even deadly snakes, however, frequently fail to inject a lethal dose of venom and the failure to realize this fact accounts for the extraordinary claims made for the effectiveness of what must constitute the most grotesque medley of remedies and therapeutic procedures inflicted on mankind. The snake stones, incantations and herbs utilized by snake charmers in India might be cited as illustrations.

As a general rule it may be stated that the colubrid snakes, which yield highly toxic venoms and kill by a curari-like paralysis of the respiratory muscles, possess a poor inoculation mechanism, whereas the vipers, which have an excellent inoculation mechanism and kill by peripheral cardiovascular shock and internal hæmorrhage, produce less deadly venom, though its local digestive action on the tissues at the site of inoculation is often intense.

The absorption time of a certainly lethal dose as determined by experiment.—Acton and Knowles [6] injected 100 mgm. of cobra venom into the tips of the tails of four dogs and amputated them 7·5 cm. above the site of inoculation at one minute intervals. All the animals died within a period of from forty-five to eighty-five minutes. Later, they repeated the experiment with monkeys, injecting 24 mgm. of cobra venom (10 M.L.D's.). With this smaller dose they found it took about eight minutes for one minimum lethal dose of venom to reach the circulation. Fairley [7] found in sheep naturally bitten over the metacarpal bone by tiger snakes that ligature and excision saved life only if the ligature was effectively applied within two minutes. Similarly, in body bites, excision and suction applied at the end of two minutes failed to save life, though the death time was prolonged to thirty-six hours fifty-six minutes; in other sheep, where similar treatment was undertaken later, i.e., five and ten minutes

after natural bite, death took place in six hours twelve minutes and fifteen minutes respectively. The experiments indicate that the absorption time of a lethal dose of tiger snake venom in naturally bitten sheep is under two minutes. The size of the dose proved all-important in other experiments, for where smaller amounts of tiger snake venom (such as two certainly lethal doses) were injected, local measures such as excision and suction, even in the absence of ligature, proved effective when applied within five minutes of the inoculation.

It is evident from these experiments that, following a natural bite by a highly poisonous colubrid, only a few minutes may elapse before a lethal dose of venom has been absorbed into the circulation, and under these circumstances every minute's delay in the application of ligature is fraught with danger to the patient. When the quantity of venom inoculated approaches the order of one lethal dose, Kellaway [8] estimates on the basis of the delayed onset of symptoms that a much longer time—perhaps hours—may elapse before all the venom reaches the circulation. Under these circumstances ligature and other local measures may possibly be of some service, despite the fact that their application has been delayed for considerably longer periods of time.

(A) Local Treatment.

The principle underlying every form of local treatment is to remove, destroy, or render inert venom inoculated into the tissues before absorption of a lethal dose into the circulation, but unfortunately, owing to the rapidity with which venom is absorbed, these measures are rarely effective under natural conditions in a really efficient bite by a venomous colubrid.

(1) *Ligature.*—Snake bite generally occurs on the limbs, and in a composite group of 281 Australian cases, 56·6% were bitten on the lower extremities, and 42% on the upper extremities. Ligature, which is the most important of all local measures, is therefore generally applicable and constitutes the first step in all forms of treatment. Complete cessation of the circulation must be aimed at both in arteries and in veins.

A piece of thick rubber tubing (1·6 cm.) makes an excellent tourniquet, but, as a first-aid measure, strips of clothing may be loosely knotted around the limb and subsequently tightened by twisting with a stick. Ligature must be applied immediately around a single bone on the heart side of the bite, the thigh and the arm being the sites and never the leg or fore-arm. Intermittent application for twenty minutes, at the end of which time the limb is flushed with blood for one minute or until it becomes pink, or continuous ligature for thirty minutes or even longer may be practised.

Value of ligature.—If applied sufficiently early, ligature is of value in postponing the death-time and permitting other modes of therapy such as local incision or specific antivenene administration. Its efficacy *per se*, as a life-saving device, is dependent amongst other things on the thrombase content of the venom. Martin and Lamb [9] showed experimentally in rabbits that immediate ligature saved life even when as much as six lethal doses of tiger snake venom were injected—a result attributable to the effect of thrombase in causing local clotting of tissue fluids and adjacent vessels. After destruction of this thermolabile constituent by heat, ligature was quite ineffective, even when only one lethal dose was injected. Fairley [10] reinvestigated the problem and found that ligature consistently failed to save sheep and goats from even one certainly lethal dose of tiger snake venom. This result was attributed to the lesser degree of sensitiveness possessed by sheep and goats to thrombase, and as rabbits are known to be highly sensitive the question arises regarding the behaviour of human tissues to this constituent. The absence of post-mortem evidence of intravascular thromboses in man suggests that no undue sensitiveness to thrombase exists, so it appears probable that as far as this colubrid is

concerned nothing more can be expected from ligature in man than postponing of the death time.

(2) *Surgical procedures.*—Ferguson [11] showed that it is essential to wash the skin in order to remove dried venom before instituting surgical measures, and for this purpose a solution of potassium permanganate is useful, if available. Scarification with a lancet, either with or without the application of potassium permanganate crystals, is futile and should no longer be advocated.

Incision ($\frac{1}{2}$ by $\frac{1}{4}$ in.) may reveal the presence of broken fangs, affords an excellent index to complete stasis of the circulation induced by ligature and also permits the application of mechanical suction, but apart from these advantages its efficacy is doubtful as drainage of the fang track by a straight incision is next to impossible.

Free early excision has more to commend it, and combined with mechanical suction is the only method of local treatment likely to be helpful in body bites where it must be instituted immediately. Immediate ligature and free excision (3·0 by 3·0 cm.) down to the muscles was the only effective local treatment in sheep bitten by tiger snakes.

Amputation is only justified in finger and toe bites when the snake has been identified, where effective ligature has been immediately applied, and provided antivenene therapy is not available.

(3) *Local venesection.*—Local venesection, which depends on washing out the tissues with the patient's own blood as advocated by Kellaway [8], may be carried out in limb bites provided the patient is seen by a medical man within the first hour or two, and provided the ligature has not yet been removed. A second ligature tight enough to obstruct the venom's return, but not the arterial circulation, is applied immediately distal to the arterial ligature. An incision is then made into one of the veins draining the bitten area, and a succession of small blood lettings from this vein is carried out by loosening the arterial ligature for one to two minutes and leaving the venous ligature in position. In the adult 1 to $1\frac{1}{2}$ pints of blood can be expended in flushing the bitten part, but in the child where only a few ounces can be taken with safety transfusions from a suitable donor should be undertaken. In animals one-third to half of the injected venom can be removed in this way, and Kellaway [8] has shown that sheep inoculated with from 1·25 to 1·5 lethal doses of various Australian colubrid venoms could be saved by this procedure; larger doses, however, were invariably fatal.

(4) *Mechanical suction.*—Mechanical suction by means of a breast pump or Bier's suction glass, combined with incision or excision, has been favourably reported on by a number of different observers. Crimmins [12] recorded that in fifty-eight experiments in dogs inoculated with the venom of the diamond-back Texas rattle-snake (*Crotalus adamanteus*), whose venom contains no thrombase, ligature and incision, combined with suction by a breast-pump, was the only locally effective measure. Jackson and Githens [13] have also shown in dogs receiving several lethal doses of venom of *Crotalus atrox*, that incision combined with suction by a Bier's suction glass and irrigation of the wound with 1 to 2% saline is effective. These procedures may be regarded as useful accessories to ligature, incision and excision.

(5) *Local injections.*—After ligature, the local infiltration of the tissues with 10 c.c. of a 1 to 5% solution of potassium permanganate or gold chloride has been advocated. Unfortunately, both these substances cause necrosis and gangrene of the tissues and are ineffective in colubrid though possibly of some value in viperine bites.

More rational is the infiltration of the bitten part with specific antivenene, if it be available, especially with venoms producing intense local proteolytic and hæmorrhagic changes in the tissues. Do Amaral [14] and Besredka [15] have recently both advocated this as a method of election in viperine bites, and from every viewpoint it appears a procedure which should be more widely practised.

(B) ANTIVENENES.

Though the claims regarding the universality of the curative qualities of the "sérum antivénimeux" introduced by Calmette (1894) were not substantiated, the specific neutralizing qualities of antivenenes against their own venoms have been abundantly upheld. With few exceptions each antivenene is only antidotal against the venom used in its production, but occasionally some cross-protection is noted against venoms of allied species. Thus tiger snake antivenene affords one-tenth the protection against Australian copper-head venom which it manifests to tiger snake venom and a monovalent antijararaca serum produced at Butantan Institute in Brazil from the venom of *Bothrops jararaca* is reported to be as effective as Calmette's serum E.R. in neutralizing the venom of the European viper, *V. aspis*.

As a general rule, however, any cross protection afforded by a specific antivenene is not sufficiently powerful to confer on it practical therapeutic value with respect to snake-bite by snakes of allied species.

Antivenene productions.—It follows from these facts that each country must produce antivenenes against its own species of snakes and the necessity for this is being increasingly appreciated, especially as modern work has tended to show the limitations of all forms of local treatments under field conditions.

Monovalent, bivalent, or polyvalent antivenenes are now available for snake-bite cases in Europe, India, Africa, Japan, Java and Australia, as well as in the United States, Brazil, the Argentine and Central America.

Under natural conditions the biting snake often remains unidentified and where several poisonous species abound, polyvalent antivenenes become necessary. Such antisera tend to be over-bulky for intravenous and intramuscular injection, and, in consequence, any effective method for increasing their potency by concentration of the pseudo-globulin fraction of the serum becomes a matter of importance. Success in this direction has already been attained with certain antivenenes. More recently Grasset [16] has reported a twofold concentration of antivenene serum against African Viperidæ and Colubridæ, 1 c.c. of which neutralizes either 10 mgm. of *Bitis* venom or 1·8 *Naia* venom, while Maitru, Naidu and Ahuja [17], record having obtained a threefold concentration of the Kasauli bivalent venom, so that 1 c.c. of the concentrated product neutralized 3·0 mgm. of Russell's viper and 1·5 mgm. of cobra venom.

Another serious handicap has been the cost of antivene production, the toxicity of ophidian venoms making the manufacture of high titre antivenoms from horses a long and hazardous affair. Detoxication of venom with simultaneous preservation of its antigenic properties has not been very successful in the past, but the recent reports of Grasset and Zoutendyk [18] from the South African Institute of Medical Research dealing with detoxication of snake venoms and rapid methods of antivenomous vaccination and serum production read much more optimistically. These observers report that concentrated solutions of viperine and colubrine venoms are readily detoxicated at 37° C. by means of formalin, the atoxic derivative being potently antigenic. By the hyperimmunization of horses, both monovalent and polyvalent antivenenes of exceptional potency were obtained with ease and safety in a few weeks, and donkeys were actively vaccinated by a course of three or four subcutaneous injections.

Administration and dosage.—Snake venom being more diffusible than antivenene is much more rapidly absorbed from the subcutaneous tissues. Martin [19] in 1899 found tiger snake antivenene had to be given in ten to twenty times the amount when the subcutaneous was substituted for the intravenous route to yield an equivalent protective effect. It follows, therefore, that after bites from highly venomous snakes, antivenene should be given intravenously, though when dealing with less venomous species concentrated antivenenes given intramuscularly, as in

the United States, appear to yield satisfactory results, provided that they are given early and that the case is one of only average severity. Severe cases should, however, always receive antivenene intravenously. Kellaway and Morgan [20] point out the danger of anaphylactic shock in persons hypersensitive to horse serum, and except in the most severe cases where delay is unjustifiable advises testing the patient for hypersensitiveness. If this be found, rapid desensitization may be obtained by giving 0·025 c.c., 0·1 c.c. and 1·0 c.c. of serum subcutaneously at half-hour intervals; in the absence of symptoms a slow intravenous injection of antivenene may be given.

Naturally, antivenene should be administered at the earliest possible moment. Analysis of the death time in fatal cases shows that the period following the bite is generally adequate. Thus, in 81 cases of fatal bites by Australian colubrids, only 15 died within six hours of being bitten. Acton and Knowles [21] state that delay is not as prejudicial as most writers claim, since in cobra poisoning the same dose of antivenene which saves life when given immediately after the bite, will still save life if given within two-thirds of the death time. Grasset [22] has recently restudied the question in sheep inoculated with Cape cobra venom, but finds that the longer antivenene is withheld, the greater is the dose required to save the animal. Further, the early application of a tourniquet enabled the effective dose of serum to be reduced to one-half or one-third by its localizing influence, which largely compensated for the initial delay in antivenom administration.

In actual practice it is well to remember that a patient is never too near death to receive a large dose of specific antivenene intravenously, should this be available. Experimentally it has been shown that the curari-like action of colubrid venom at the neuromuscular junction is a reversible one, and this is borne out clinically by the recoveries recorded in profoundly paralysed patients.

The actual dosage will depend on the titre and concentration of the antivenene, the severity of the symptoms, and the size and venomosity of the snake implicated. The distance between the fang punctures may afford useful information. Generally, dosage is given in inverse proportion to body-weight so that children may require several times the amount of venom which would be life-saving in an adult. Finally, it may be pointed out that injections of antivenenes may need to be repeated, especially in children, and that in colubrid bites paralytic symptoms may reappear after apparent recovery. For this reason all cases should be kept under careful medical observation for at least twenty-four hours, the patient being repeatedly examined for reappearance of symptoms during this period.

The value of antivenene.—No observer who has studied snake bite clinically can fail to be impressed with the dramatic results following the intravenous administration of specific antivenene in adequate dosage, but statistical data on this subject are practically unobtainable. Indian records are valueless for the purpose, and figures from most countries are unsatisfactory, owing to the meagre nature and unreliability of the information available. It has, however, been estimated that the death-rate of persons in Brazil receiving antivenene has been reduced from 25 % to 2·5 %, while Hutchinson [23], in an analysis of snake bite cases occurring in the United States in 1928, records a 10·8 % mortality in 175 cases receiving no antivenene, compared with a 3·0 % mortality in 433 cases receiving their standard polyvalent concentrated antivenene specific for the rattle-snake, copper-head and moccasin. Most of the cases in this series appear to have received antivenene by the subcutaneous route.

When we come to consider the protective action of antivenene on different species of laboratory and domestic animals receiving multiple lethal doses of venom, we are on surer foundation, and its demonstrable protective power under these circumstances, plus clinical experience of equally striking cures in man, constitute irrevocable evidence regarding its life-saving properties.

(C) General Measures.

General measures include absolute rest and reassurance of the patient. Natives have been recorded as dying of psychical shock following the bite of a non-poisonous snake. Similarly, the old method of keeping a patient moving in order to avoid the onset of paralysis, was very fallacious, since exercise increased the circulation in the limbs and so accelerated the absorption of venom.

Warmth and stimulants, such as hot black coffee, caffein citrate, or injections of camphor in olive oil may be given, but strychnine and alcohol are better avoided and morphia is definitely contra-indicated.

Circulatory shock may be treated along general lines by giving the patient plenty of fluid, per os if swallowing is possible, otherwise per rectum. Pituitrin and adrenalin are useful and such measures as bandaging the limbs and elevating the foot of the bed should not be forgotten.

Respiratory failure is treated by artificial respiration, and it is important to keep the mouth and nasopharynx free from mucus and to prevent vomitus from entering the larynx if vomiting occurs.

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Discussion

Colonel R. H. Elliot said that the characteristic feature of the Viperidæ was erroneously supposed to be that they alone had "erectile" fangs. In Madras he had used a large quantity of snake venom, but could not keep a number of live snakes for milking purposes. His snakes were chloroformed and nailed down on a board, and then the blood and bile were drawn off; finally the poison sacs were dissected out and their contents squeezed into sterile watch-glasses, when the venom was dried in vacuo and then stored. During this process he learned repeatedly and conclusively that tickling the mucous membrane of the snake's mouth led to a marked erection of the poison fangs. On the cessation of the stimulus the fangs fell to their natural position of rest, folded back against the roof of the mouth. He failed to see how, were it not for this arrangement, the fangs could escape being broken off short each time the snake took a bulky meal.

The real remedy for snake bite was undoubtedly an antivenene. The brand of this must vary according to the nature of the snake which had bitten the patient. (1) The snake often made its escape, and its variety was then unknown. The native—all the world over—called every snake "one very bad snake, Sahib." Even an expert found it difficult, if not impossible, to identify a snake making off in the brushwood. Therefore an antivenene was needed which would cover all the snakes of the particular neighbourhood. (2) The remedy must be fresh and in sufficient quantity. Here came in the question of expense and of

organization for the distribution of the remedy. (3) To be effective in a severe bite and hours after the bite, intravenous injection was almost imperative, and this practically demanded administration by a medical man, and a skilful one at that. (4) The potency of the remedy must be very high. Much had been done in this direction during recent years, but it was a matter which required constant and careful supervision. In the early days, and possibly at some centres still, the commercial side of the question had been allowed to overshadow the scientific. Unfortunately "cures," widely advertised, had helped the sales and been a source of profit, whereas a careful analysis of the facts would have led to a doubt (1) whether the snake was truly of a dangerous species, and (2) whether a fair bite had been inflicted. He (the speaker) was not disputing the value of antivenenes, but was urging that they should only be prepared under strict scientific supervision.

A good deal had been written on the subject of immunity acquired by the snake men. It had been said that they rubbed the poison into the backs of their hands and forearms, and that by doing so they acquired some measure of immunity. What was known of the mongoose certainly lent support to this, for it chewed up the head of the snake, and apart from what it swallowed, it must get, from time to time, some of the venom absorbed through breaches in the mucous membrane caused during the fight. He (the speaker) had found the immunity of the Indian mongoose to be twenty-five times that of a rabbit. Calmette, working on mongooses obtained from Guadeloupe which had been away from poisonous snakes for twenty-five years—corresponding to about fifty generations—found their resistance only eight times as great as that of the rabbit. Thus it seemed that the immunity had fallen considerably during this comparatively short period. While working on snakes he (Colonel Elliot) had tried hard to get reliable evidence as to the immunity acquired by snake men, but had never been really satisfied on the subject. Two of the men who collected venom for him had died as the results of bites, the explanation being that they were getting far more money than they had ever been accustomed to do, and that, in consequence, they had indulged too freely in native spirit, which caused them to lose their habitual caution. They had made some sudden movement, which frightened the animals and caused them to strike, with fatal results. In the South of India, at least, the snake men knew no method of scientific immunization by gradually increasing the doses they employed. He (the speaker) would not venture to generalize from this for the rest of India, but would certainly not be satisfied to the contrary without very clear evidence.

A point to which he would draw special attention was the possibility of utilizing snake venom pharmacologically. The most dangerous drugs had always been the most powerful remedies, but only when they were harnessed and brought under thorough control. The separation of the different poisons from each other and the careful study of their individual actions must long precede any effort to use them clinically. Over thirty years ago he had drawn attention to these possibilities; to-day they seemed more than ever before to be coming into the sphere of practical politics.

Colonel F. P. Mackie: The Registrar-General's mortality returns for India show that on an average about 20,000 deaths from snake bite occur annually in India, and one would suppose that it would be easy to get adequate statistics regarding the use of antivenene or other remedy. This is, unfortunately, not the case as, after a survey of the published cases in India during the last thirty years, there is little evidence on which reliable clinical statistics can be based. By far the greater number of cases never come under European treatment; for instance, in 1908, in one small district in Bengal there were 363 fatal cases reported of which only two were taken to dispensaries. Even of these small numbers the majority come under observation only after native remedies have failed and the patient is beyond recovery. In many instances a preliminary trial is made with some local application, such as potassium permanganate, and even when antivenene is used, it is rarely given in adequate doses, on account of its price and the small amount kept in stock in the mofussil dispensaries. In many cases too the snake is not seen or identified, so that the case records become weighted by the inclusion of non-venomous bites. Thus there are many reasons why it is difficult to give satisfactory figures.

Acton and Knowles computed that not more than 10 or 15% of persons bitten by snakes received a fatal dose and this is supported by statistics collected by Clarkson, who reported 263 cases in one district of Bengal of which 81% recovered; and 170 in another out of which 139 recovered—again 81%. It is true that both these groups included those who had received local applications of potassium permanganate from the village watchman or other minor

official, but as we shall see later, treatment by antivenene thus administered, is not likely to reduce the mortality substantially.

The Indian villager regards snake bite as synonymous with death, and as a result of this there are an enormous number of remedies, some dating from very early times and having a great reputation as cures.

Returning to the use of antivenene some statistics were collected by Colonel Dennys relating to cases in which the snake was known to be venomous and out of 39 such cases, 25, i.e. 64%, recovered after treatment by antivenene while of 20 treated within two hours of being bitten one half died despite antivenene.

He concludes that antivenene given intravenously more than two hours after the bite, and where symptoms are advanced, is likely to be of little use; but when given within two hours of the bite, even when symptoms are far advanced, may result in rapid recovery, but even in such favourable conditions death is by no means always averted. Nevertheless, he advocates the use of the remedy in cases in which not longer than four hours has elapsed since the bite. He emphasizes the use of the intravenous route, other possible routes being too slow. In this connexion, Acton and Knowles found that the rapidity of action by the subcutaneous, the intraperitoneal, and the intravenous, routes was as 1 : 2 : 4 in the case of cobra venom and 3 : 8 : 8 in viperine venom. They also state that cobra venom is absorbed rapidly from the site of injection but enters into combination with the nerve-cells loosely and can be dissociated by antivenene up to two-thirds of the death period, whereas viperine venom is absorbed more slowly but becomes attached more firmly to the endothelial cells of the vascular system, and therefore antivenene, to be effective, must be given at once. Another factor of profound importance in judging the result of treatment is what constitutes a lethal dose and how many such doses a given species of snake is capable of giving.

Acton and Knowles state that the fatal dose for a man is, for the cobra 15 mgm., the krait 1 mgm., banded krait 10 mgm., Russell's viper 42 mgm. and the echis 5 mgm., and that these snakes when tested in the laboratory yield several or many lethal doses at a bite. In the case of cobras and hamadryads this amounts to about ten lethal doses for man, for the krait five lethal doses, and for the Russell's viper and the echis only two, so that in many cases, particularly with the last two snakes, a lethal dose may not be given. Amongst local remedies oxidizing agents such as potassium permanganate have been most favoured. No little controversy has arisen as to the effects of such remedies and at one time this remedy was the vogue in India and the lancets devised by Lauder Brunton were issued to village constables and other minor officials in Indian villages. Laboratory investigations, by Bannerman on dogs and by Acton and Knowles on smaller animals, completely failed to substantiate the claims made for its use in the field. This form of treatment has largely fallen into disuse, and the most that can be claimed for it is that given a very early case when the venom is still in situ, followed by firm ligation and a very free opening up of the region of the bite, the application of a strong solution of a permanganate may destroy such venom, as it can combine with it and may convert a lethal into a sublethal dose. If antivenene is available, this local application should be avoided as it may increase the tendency to necrosis and sloughing which is in any case liable to follow viper bites.

In a country where the cobra is an object of veneration and even of worship as an incarnation of Shiva it is not to be wondered at that an immense folk lore and manifold superstitions should have grown up around the subject of native remedies.

The Haffkine Institute achieved a great notoriety in connexion with the subject, firstly because we kept a large stock of living snakes from which the venom was expressed *coram populo*, and also because we gave free antivenene treatment to all comers, and so it was natural that all who had infallible cures would bring their claims to be tested by us. Scarcely a week passed in which we were not asked to experiment with some remedy or other, and we nearly always allowed the claimant to apply his own remedy in any way he wished to a dog which we had caused to be bitten by a cobra. Never once was death prevented or even delayed by any remedy.

In order to stop this spate of so-called " cures " Caius and Mhaskar took up the scientific investigation of all the drugs of the indigenous pharmacopœia to ascertain whether any of them had any power to avert or postpone the fatal issue in dogs injected with lethal doses of cobra venom. They tested 314 individual drugs and 184 combinations of these, using four dogs for each drug after adjusting the venom dose that it should not kill in under two hours.

Their conclusions, in their own words, were that " None of the Indian plants recommended for the treatment of snake-bite has any preventative, antidotal or therapeutic effect."

Extraction of the venom by suction has a time-honoured place in the history of snake-remedies, whether by the mouth of a heroic companion or by various kinds of sucking implements, but I must refer to a method well recognized in India known as the "Fowl cure." It is best described in the words of an assistant surgeon who witnessed it.

> "I found nineteen chickens heaped on the ground (around the patient) and one was applied in the following way in my presence. The feathers having been peeled off from around the anus of a live chicken, it was made to sit on the wound, that is the anus was applied to the wound whilst a man was holding it in his hand over the wound. After five or six respiratory efforts it first began to doze, pupils upturned, and then the head gradually fell down upon the chest; it seemed to shake off its drowsiness twice or thrice and inspired again and so imbibed fresh poison. Then the intervals between inspiratory efforts became longer till at last its head fell on to its breast, beak remained permanently open, and so expired. It took about five minutes to die. Notwithstanding the death of these twenty chickens, the patient's condition was getting worse and worse."

The doctor then gave 20 c.c. of antivenene and the patient began rapidly to recover. He continues in the true scientific spirit:—

> "So an experiment was made with two chickens successively by placing their *ani* one after another on the wound and keeping them there for fifteen minutes. The moment they were let loose they flew away to a distance," and from this he concludes that there was no more venom left in the wound.

Another Indian doctor (1928) records a similar case in which 96 chickens were used of which "the first 74 died, the next 12 became half dead but recovered and six lost consciousness but recovered. Most of these chickens died in three minutes."

Alas for the possibilities of this wonderful cure: A sceptical I.M.S. officer records that "chickens die equally obligingly after the bite from a non-poisonous snake and they are induced to do so by asphyxia brought about by the operator's hand."

Colonel Elliot (in further comment) said that very little stress should be laid on the Indian statistics of death from snake bite. They probably covered up a good deal of murder, and from a scientific point of view they were very unreliable. At the same time, owing to the habits of the people, death from snake-bite was comparatively common all through the East.

He could endorse Dr. Hamilton Fairley's statement about the quick result of the viperine bite. He (the speaker) had once persuaded an Indian pie-dog to walk over a Russell viper by throwing pieces of meat in its neighbourhood. The viper became annoyed, seized the dog under the belly and shook it as a terrier shakes a rat. The dog yelled, but was none the worse. Three days later, the same dog walked over the same Russell viper for bits of meat. The viper's head shot up like the crack of a whip and the dog was dead in less than twenty minutes.

He (Colonel Elliot) believed that venom obtained, as he had obtained it, from the sacs of freshly killed snakes, approached more nearly to that used under normal conditions of bite than the venom milked out in the usual way. So far from the venom sacs being empty, as had been suggested, they were almost invariably distended with the poisonous fluid.

With regard to the low toxicity of the Russell viper's venom, one reason for that might be that the poison was so fluid—much less viscid than that of the cobra, for instance. Presumably its solid contents were relatively low.

The only case in which he (the speaker) had used a ligature was his own. When nailing down a snake he had carelessly allowed his thumb to slip down on to its tooth from which venom was streaming out. He believed that he had a ligature applied within fifteen seconds. He had an incision made down to the bone and packed it with potassium permanganate, releasing it at intervals. The procedure was very painful but he had no symptoms of snake-bite. He attributed this fact to the quick ligation, to the small dose of venom and to his having been able to get potassium permanganate into actual contact with a large part of the area into which the venom had been injected. He did believe in the Lauder Brunton outfit. He preferred to use a good penknife and to cut down freely and then to pack the wound tight with potassium permanganate, disregarding the risk of local necrosis.

Section of the History of Medicine

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William Harvey's Knowledge of Literature—Classical, Mediæval, Renaissance and Contemporary

By D. F. Fraser-Harris, M.D., D.Sc., F.R.S.E.

Unless we happen to have considered the subject, we can have no adequate notion of the extent of Harvey's acquaintance with Classical, Renaissance and Contemporary Literature. We are, perhaps, too apt to think of William Harvey as the author of that *libellus aureus*, the *De Motu*, and forget that he also wrote the *De Generatione*, on "Parturition," on the "Uterine Membranes and Humours," and on "Conception," throughout all of which he displayed the most intimate knowledge of the works of many authors who had views on topics of biological interest germane to the matters under discussion,[1] nor should we forget the lost writings of Harvey on Medicine, Pathology, Respiration and Insects.

Besides the works just mentioned, Harvey composed two "Disquisitions" to Riolanus, full of references to Galen, and nine letters to contemporaries which have come down to us—one to Caspar Hofmann, of Nuremberg; one to Paul M. Slegel, of Hamburg; three to John Nardi, of Florence; one to R. Morison, of Paris; one to J. D. Horst, of Hesse-Darmstadt and one to John Vlackveld, of Haarlem. It is in the letter to Morison that Harvey has so much to say of Pecquet of Dieppe, the discoverer of the Receptaculum Chyli.

There seems no room for doubt that Harvey could read in the original the Greek and Latin authors to whom he refers.

Of Greek writers he mentions no fewer than twenty-five ranging from Thales of the seventh century B.C. to Suidas, the reputed author of a Greek lexicon, who flourished about A.D. 975. These authors are—of the seventh century B.C.: Thales; of the sixth: Pythagoras, Alcmaeon of Crotona, Anaxagoras, Heraclitus, Epicharmus of Syracuse, and Diogenes of Apollonia; of the fifth century: Empedocles, Hippocrates, Socrates, Polus, Critias, Plato, Democritus of Abdera, Eudoxus of Cnidus, Euclid of Megara and Erasistratus; of the fourth century: Aristotle, Epicharmus and Menander.

The following who wrote in Greek belong to the Christian era: Palladius, Galen, Plutarch and Suidas.

Fourteen Latin authors are quoted or referred to by Harvey, namely: Virgil; Varro; Seneca; Terence; M. A. Apicius; the elder Pliny; Lucius Papyrius; Celsus; L. J. M. Columella; Domitius Ulpianus; Quintus Serenus; Florentius; Pipinus and Migaldus.

Three names belong to the Middle Ages, two Arabic writers, Avicenna and Averröes and the schoolman, Albertus Magnus.

When we come to Renaissance and Contemporary writers, the list is even more imposing. It comprises thirty-two names. Of writers born in the fifteenth century

[1] The edition used in this research is, *The Works of William Harvey*, translated by R. Willis, M.D., London, The Sydenham Society, 1857.

we have: Jacobus Sylvius[2]; Fracastorius; J. C. Scaliger and Andreas Laurentius. Of authors in the sixteenth century there are: Fernelius; Vesalius, Eustachius; Fabricius; Realdus Columbus; J. C. Arantius; Leonardus Botallus; Franciscus Valesius; Caspar Bauhin; Volcherus Coiter; Ulysses Aldrovandus; Descartes; Hollerius; Caesar Cremoninus; Gasparo Aselli; Fortunius Licetus; Spighelius; Thuanus (J. A. de Thou); Gregorius Nymannus; Josephus Aromatorius and Daniel Sennert.

Of writers born in the seventeenth century we have: Pecquet of Dieppe; Walaeus of Leyden: Thomas Bartholinus and Johannes Riolanus; and two authors whose birth dates have not been ascertained, Du Val of Rouen and Aemilius Parisanus of Venice.

In the manuscript notes to his Lectures, Harvey refers to eight writers whom he mentions nowhere else: Plautus, Horace, Julius Cæsar, Cicero, Vitruvius, Nicholaus Massa and Archangelo Piccolhomini.

We may summarize the numbers of the authors quoted in Harvey's published and unpublished works thus:—

Of Greek authors	25
Of Latin authors	14
Of Mediæval authors	3
Renaissance and Contemporary	32
In MSS. of Lectures	8
Total	82 authors.

While the great majority of the references in Harvey's writings are to subjects of biological importance, this is not exclusively the case. As early as at the end of the first chapter of the *De Motu* we have seven lines introduced by, "as the old man in the comedy says." The lines are:—

> "For never yet hath any one attained
> To such perfection, but that time and place
> And use have brought addition to his knowledge,
> Or made correction or admonished him,
> That he was ignorant of much which he
> Had thought he knew; or led him to reject
> What he had once esteemed of highest price."

These lines are the translation of a speech by a character "Demea" in Act V, Scene 4 of Terence's play, *The Adelphi*.[3] Demea is an old married man who is contrasting his bachelor brother's care-free existence with his own life of worries.

Harvey is known to have been very fond of *Virgil*; his expression, "Everything if full of Jove" is a reference to "Jovis omnia plena" in Virgil's third *Eclogue*. Harvey quotes from Virgil four times in the *De Generatione* and once in the essay on "Parturition," but in no case is the precise poem cited, although Virgil is named on three occasions.

Two of the references are to the second book of the *Georgics*, the first of which (*De Generatione*, p. 187) is a quotation of eight lines of some translation, and is prefaced by, "Whence the poet sings"—

> "Earth teems in Spring and craves the genial seed.
> The almighty father, aether, then descends
> In fertilizing showers into the lap
> Of his rejoicing spouse, and mingling there
> In wide embrace sustains the progeny
> Innumerable that springs. The pathless woods
> Then ring with the wild bird's song, and flocks and herds
> Disport and spend the livelong day in love."

[2] In almost every case Harvey uses the Latin, rather than the native, form of the names of Renaissance writers.

[3] This passage was found for me through the kindness of Professor Singer.

The second quotation from the second *Georgic* is in the essay on "Parturition" (p. 543), and here Virgil is named thus—"to use Virgil's expression with reference to the fields:—

> 'Superat tener omnibus humor
> Et genitalia semina poscunt.'"

These words (which are not translated) occur in lines 331 and 324 of the second book of the *Georgics*.

The third allusion to Virgil is to a passage in the second book of the *Æneid* (lines 330 and 331) which relates to the west wind (*De Generatione*, p. 219)—"Varro declares that the mares in Lusitania conceive by the wind. For Zephyrus was held to be a fertilizing wind, whence its name as if it were ζωηφερος, or life-bringing. So that Virgil says:—

> "And Zephyrus with warming breath resolves
> The bosom of the ground, and melting rains
> Are poured o'er all, and every field brings forth."

The fourth quotation from Virgil and the third in the *De Generatione* (p. 282) is in reference to the universality of a vital principle or soul in all living things. In this case Virgil is not named; Harvey remarking, "We exclaim with the poet—

> "'Tis inmost soul sustains, and mind infused
> Through every part that actuates the mass."

This is from a passage in the sixth book of the *Æneid*.

Harvey's fifth reference to Virgil and the fourth in the *De Generatione* (p. 507) is the only one in which both the Latin original and a translation are given—(tenth book of the *Æneid*, line 847)—

"The blood is the living principle of man," says Suidas; and the same thing is true of all animals; an opinion which Virgil seems to have wished to express when he says:—

> "Una eademque via sanguisque animusque sequuntur";
> "And by one path the blood and life flowed out."

As we might expect in treatises of biological import, Aristotle is the author most often referred to; in fact 269 times in all, 230 times in the *De Generatione* and 21 times in the *De Motu*.

In thus quoting so much from Aristotle, Harvey was but acting on his own advice, for in a notable conversation with Aubrey he had said: "Go to the fountain head and read Aristotle, Cicero and Avicenna" (a Greek, a Roman and an Arabian).

A great deal of the *De Generatione* is taken up with discussions about the soul and its relation to the blood. On this subject Thales, Diogenes, Heraclitus, Alcmaeon and Suidas are all quoted.

Anaxagoras and Hippocrates are referred to as believing that the chick arose from the yolk or vitellus but was nourished by the albumin called by Anaxagoras "bird's milk" (ὀρνιθος γαλα). The following passage from the *De Generatione* (p. 212) is typical of the kind of aspect under which the ancients viewed this and similar topics: "The vitellus," says Fabricius, "is so called from the word *vita* because the chick lives upon it; from its colour it is also spoken of as the "yellow" of the egg, having been called by the Greeks generally, χρυσὸν; by Hippocrates, χλωρὸν; and by Aristotle ὠχρὸν, and λεκυθὸν; the ancients such as Suidas in Menander called it νεοττὸν, i.e. the chick, because they believed the chick to be engendered from this part." This passage is a careless translation of Harvey's Latin so far as the reference to Suidas is concerned—"quod Suidas ex Menandro scribit." Suidas in his *Lexicon* quoted from the *Andria* of Menander a passage whose translation is: "and after this give her the yolk of four eggs." The word yolk, το νεοττιον, is the same as the Greeks used for a young bird or nestling.

[This is the same Menander from whose lost play, *Thais*, St. Paul quoted in 1 Cor. xv. 33 the words, "evil communications corrupt good manners," the context being that the behaviour of the prostitute Thais was so disgraceful that to know her was to be corrupted.]

Indeed the nourishment of the embryo and of the fœtus occupies a good deal of Harvey's attention in *De Generatione*. Democritus of Abdera is quoted on this subject; but in pre-microscopic days it was an insoluble problem.

In the essay on "Conception," the problems of resemblance to parents and like begetting like are the occasion of much thought; Socrates, Plato, Aristotle and Epicharmus all being drawn upon for light.

Harvey was, of course, perfectly familiar with the works of Galen which he probably read in some Latin edition. But one must place Galen amongst the Greek authors seeing that he wrote in that language: he is quoted 26 times in the *De Motu*, 13 in the *De Generatione*, and 59 times in all throughout the Harveian writings.

Galen's name occurs as early as the second paragraph of the Introduction to the *De Motu*. In Chapter V Harvey speaks of "the divine Galen" and of "this father of physic," and Galen is quoted more frequently in the *De Motu* than any other author.

Harvey refers to no fewer than 32 Renaissance and Contemporary writers from Jacobus Sylvius of Paris to such contemporaries as Descartes and Lord Verulam. Indeed, Bacon is the only Englishman from whom he quotes, and that is just a phrase, "to enter upon our second vintage" (*De Generatione*, p. 270) "in the words of the learned Lord Verulam."

Vesalius, Harvey quotes twice and both times to differ from him. He calls him, "the great Vesalius." It is pleasant to remember that Vesalius, the Father of Anatomy, was half an Englishman, inasmuch as his mother Isabella Crabbe, was an Englishwoman. To Hieronymus Fabricius Harvey refers very often; he calls him "my old teacher" as indeed he was at Padua between 1598 and 1602.

Where Harvey agrees with Fabricius is not when he is dealing with the valves of the veins but with his views on topics concerning the physiology of reproduction.

Two well-known names are conspicuously absent from among the authors whom Harvey quotes—Michael Servetus and Andreas Caesalpinus. Servetus was doubtless not quoted for the sad but excellent reason that all except [three copies of his *Christianismi Restitutio* were burned at the foot of the stake at Champel near Geneva, where their author perished in October 1553. Columbus is supposed to have learned from Servetus of the pulmonary transit of the blood, and Harvey quotes Realdus Columbus on that subject (*De Motu*, pp. 15 and 41)—the point under discussion being the improbability of a vessel of the size of the pulmonary artery merely carrying nourishment for the lungs.

But Harvey's silence regarding Caesalpinus is much more remarkable, Caesalpinus whom in Italy even to-day many physiologists regard as the discoverer of the circulation of the blood. This omission cannot have been due to Harvey's not having known of the writings of Caesalpinus who died in 1603, seeing that Harvey quotes from many writers so much more obscure than Caesalpinus of Arezzo. But in truth Caesalpinus was very well known. He was a distinguished Botanist and first Keeper of the famous botanical garden at Pisa founded in 1543. At the University of Pisa he was Professor of Medicine from 1567 to 1592, when he went to Rome as Professor of Medicine at the Sapienza and as Physician to the Pope, Clement VIII. Seeing that Caesalpinus wrote voluminously in his *Questiones Peripateticae*, we can only conclude that the judicious Harvey found in all his disquisitions nothing of any real value concerning any problem of the circulation.

In 1911 I dealt so fully with the supposed claims of Caesalpinus to be regarded as the discoverer of the circulation of the blood, that I shall here only refer to these papers: "Harvey versus Caesalpinus, the controversy re-opened" (*Edin. Med.*

Journ., August 1911) and, "Harvey and Caesalpinus, the controversy continued" (*Proc. Inter. Cong. Med.*, 1913, Section XXIII, History of Medicine); which was a reply to Dr. G. Bilancioni, then of Rome, in *Archivio di Fisiologia*, X. IV., May 1912.

The First Immunologist, James Pylarino (1659-1718), and the Introduction of Variolation.

By C. N. Alivisatos, M.D.

Variolation, that is, preventive smallpox inoculation, is the first immunizing method introduced into medicine. James Pylarino in 1701 inoculated with smallpox virus the three children of a friend, with the object of giving them a mild attack and thus preventing a severe occurrence of the disease. He inaugurated that brilliant method to which is due the saving of so many lives, a method which developed with Jenner's vaccination and reached fuller fructifications with Pasteur's and Almroth Wright's injection with attenuated microbes and toxins.

The earliest history of variolation is obscure. It was in use among popular healers in the Far East and thus was transmitted to Greece. The introduction of the method into medicine by Pylarino was effected by the study of this popular empiricism. So also Jenner, after studying popular procedures, introduced the method of vaccination.

Although the name of Pylarino and that of his collaborator Timoni is found in most histories of medicine, the place accorded them is perhaps not adequate. This is due to the advent of vaccination which caused variolation to be forgotten. But variolation is not only a great prodromic discovery of Jenner's vaccination but also was the means of saving a great number of lives during the eighteenth century. This was emphasized in 1754 when the Royal College of Physicians of London declared variolation to be "highly salutary to the human race."

Pylarino was born in 1659 at Ithacurie, a town in the largest of the Ionian Islands, Cephalonia, the ancient kingdom of Ulysses, an island then giving to Greece, Italy and eastern Europe many prominent scholars and physicians. He studied at the University of Padua, first law, obeying the desire of his parents, and later medicine, to follow his own inclinations. At 16 he was proclaimed Laureate in law, and at 20 Doctor of Medicine.

A real Cephalonian, Pylarino was a wanderer. Soon after his qualification he was in Crete, where governor Ismail Pasha appointed him head court physician. Later he went to Moldowallachia, comprised in the Rumania of to-day, and became head physician to the governor of the province, Prince Cantacuzene. Three years later he travelled in Germany and on to St. Petersburg, where he was appointed physician to Peter the Great. He soon left Russia, being unable to endure the cold, and went to Serbia, where he was physician to the Prince of Serbia. In 1701 he settled in Constantinople and began to study variolation. Next he practised for a time in Smyrna, where he was nominated consul to the Venetian Republic. In 1715 he returned to Italy for a consultation about his health and to publish his book. Having the satisfaction of seeing his method generally accepted, he died in Padua in the year of his return and is there buried in the church of St. Francis. Apart from his work on variolation published in 1715 he left some other writings amongst which *La Medicina Diffesa* was published in Venice in 1717.

Pylarino had a great reputation as physician in eastern Europe and Italy. P. Niceron in his *Mémoires pour servir à l'Histoire des Hommes illustrés de la République des Lettres* (1727-1747) counts him amongst the most illustrious contemporary physicians. Zeno wrote his biography and J. Morelli calls him "uomo di vasto genio e di talento perspicasissimo."

The name of Emanuel Timoni should be remembered together with that of Pylarino for the introduction of variolation. We know little of his life. He was born in Chios in the later seventeenth century and took his M.D. at Padua and

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NOVA ET TUTA

VARIOLAS

Excitandi per Tranſplantationem Methodus;

Nuper inventa & in uſum tracta:

BL. del ILCONTE DON.

Qua ritè peracta, immunia in poſterum præſervantur ab hujuſmodi contagio Corpora.

A Jacob Pylarino

VENETIIS, MDCCXV.

Apud Jo. Gabrielem Hertz.

Superiorum Permiſſu.

Je a reimprimé ce Traité à la Haye sous ce Titre: Bini Tractat de nova Variolat per transplant. maitrani methodo quam privat ex Ventre exemplari, alter vero ex Transactionib. Philosoph. Anglican. Lugd. Batav 1721. 8. 48. 80
Lyd. traité sur une Relation d'Eman. Timoni à la Société Royale

somehow acquired also an Oxford degree. For a certain time he was professor at Padua. He came in touch with Pylarino probably in Smyrna. He communicated a paper on variolation to the Royal Society in 1713 (printed in 1714) and was thus

the first to write on the subject for western physicians. This of course gives him no priority, for Pylarino began the study of variolation in 1701 and, although his book was not published till 1715, it embodies researches which had started long before.

In 1725 Timoni was living in Constantinople. Seigneur A. de la Motraye, who visited Constantinople at this time, met Timoni there and learned from him many details about his paper to the Royal Society and his later publications. Tronchin says that in 1741 Timoni was physician to the sultan of Constantinople.

Anthony Timoni, son of Emmanuel, was also a physician in Constantinople. In his *Dissertation sur l'inoculation de la petite vérole* (1762) he tells of the work of his father without, however, mentioning Pylarino. He relates how his sister, although inoculated, died of smallpox, and adds that this was because it was many years since she had been inoculated and that the effect must have diminished with time. "As far as man can remember amongst thousands of people to whom artificial smallpox had been given only two had the disease a second time." The two negative cases are those of his sister and of a small boy who had been inoculated at the age of 11 months and, seven years later, contracted smallpox from which he died.

The inoculation of smallpox for the prevention of a severe outbreak of the disease was a popular measure in China and Persia. It was introduced among popular healers into the provinces of the Ottoman Empire, notably into northern Greece and the Caucasus. It was intensively practised in particular among the Circassians who, as the younger Timoni writes, "wished to preserve the beauty of their daughters, as their great source of income, for the lovely Circassian girls were greatly in demand for the sultan's harem and the seraglios of the Turkish grandees."

Pylarino as a physician showed no contempt for the results of popular empiricism. He was not repelled by the rough handling and the atmosphere of mysticism and magic which surrounded the practice among the old women of Thessaly, in whose hands resided exclusively the method of variolation. He began to study this procedure in 1701 and by 1709 felt sufficient confidence in its results and in the technique that he had developed to practise his first inoculations. In the course of a severe epidemic of smallpox he did not hesitate to have inoculated the three children of a friend.

"The two youngest children," he says, "aged 5 and 7, showed a pustular eruption with slight discomfort, both of which had subsided by the end of a week. The eldest, aged 18, suffered more severely; the fever and eruption lasted for fourteen days."

Pylarino explained the intensity of the reaction in this case by idiosyncrasy—diathesis, as we should say to-day.

The epidemic died away, killing several in the household of the Greek merchant whose children had been inoculated, but the children themselves suffered not at all. Afterwards Pylarino performed "transplantation" in several noble Greek families of Constantinople. None of the inoculated caught the infection.

Pylarino writes in his book that although variolation was rapidly adopted by the Greek families it was only with difficulty that the Turks could be persuaded to submit to it. "The method consists," he says, "in the injection (*insertio*) of serum —*fermenti morbificis*—taken from a variolous pustule into the skin by small scratches." With regard to the technique, he says:—

"The most appropriate season must be chosen, and we recommend spring, eliminating winter. . . . The pus for transplantation must be collected with great care. The serum should preferably be taken from a ripe pustule appearing on the subject in the course of an epidemic. The subject should be young and of good general constitution. . . . The pus should be collected in a glass receptacle, as clean as possible, which should not be allowed to become cold. This receptacle should be immediately placed in the arm-pit, where the warmth of the body will allow the pus to keep a certain amount of the necessary heat during transit. . . .

Transplantation must be performed as soon as possible after collection, The subject should be placed in a moderately warm room sheltered from draughts.

"By a sharp instrument of metal or gold held horizontally in relation to the place chosen for the operation a few small incisions are made, either on the forehead at the base of the hair, on one of the cheeks or on the chin, preferably, however, on an arm or leg. The pus is then applied drop by drop to the incisions with the same instrument. The wounds are then carefully covered by a dressing. The subject must be forbidden to touch the transplanted parts and above all to avoid contact with damp. By acting on muscular regions pain and excessive local inflammation are avoided, and the regions of tendons are untouched." He emphasizes the care with which the inoculated must be surrounded. They must remain in bed for several days, and keep to a strict diet for at least forty days. Meat and bread should not be allowed. The symptoms, he tells us, vary, according to the age, idiosyncrasies and strength of the subjects. So, too, the "purulent serum" (fermenti) may differ in action, occasioning pustules to break out on the third or fourth day, or on the other hand much later. In general they appear towards the seventh day. The pustules themselves are spaced far apart, and are few in number; 20 or 30, rarely 100 or 200. They appear first on the site of the scar. They begin with slight local redness which gradually becomes covered by a phlyctenula. Rarely, this conceals purulent ulcerations, extremely painful if localized on the hands or feet. If they then open, all symptoms subside.

Finally, Pylarino admits certain failures. He foreshadows the problem of acquired immunity, saying that these mishaps may perhaps be attributed to the fact that "certain subjects show no variolous diathesis," or else to the fact that the serum was inactive, badly collected, etc. He never observed a fatal case of smallpox following transplantation, but he advocates the restriction of the practice to experienced physicians.

It is interesting to compare these passages published in 1715 but based on experience of many years, with the paper of Timoni read two years earlier before the Royal Society by the Gresham professor of physic, John Woodward.

After historical preliminaries, in which we learn that variolation had been practised in Constantinople for forty years, Timoni declares that he never had any regret for adopting it. His method differed from that of Pylarino only in minor details. Out of 50 persons inoculated by Timoni 46 developed a mild attack with but few pocks although an epidemic was then running a virulent course. In the remaining 4 cases the results came near the confluent type, but there was a suspicion that at the time of variolation those subjects were not already infected. None of the 50 died.

Owing to the work of Pylarino and Timoni variolation was practised extensively in the Ottoman Empire and was known as "the Greek method." Lady Mary Wortley Montagu arrived in Turkey in 1717 as wife of the British Ambassador. She quickly realized the value of variolation, and did not hesitate to submit herself and her child to inoculation. In a letter, dated April 1718, from Adrianople, she writes: "The pus is introduced not under the skin but into the vein; sometimes . . . into several veins at the same time. . . . Seeing the results, the person to introduce this method into England would be considered a true benefactor of his country. If I live, I shall find myself obliged to do so, even if I am to be at war with the whole medical body of my country."

Lady Mary kept her promise, and on her return to England did much to propagate the method. Although the results of variolation had already been communicated by Timoni to the Royal Society in 1714 and in an abstract of Pylarino's book in the *Philosophical Transactions* of 1716 as well as in Pylarino's book itself, it is nevertheless probable that the medical world would not have taken these researches very much into consideration had it not been for the social campaign of Lady Mary. It

is well known that the British Government was interested in the question and that six prisoners from Newgate were chosen for the first variolation. In 1722 the children of the Prince of Wales and those of Lady Bathurst were subjected to the same preventive measure.

Following Cawadias we may distinguish three periods in the history of variolation.

First period (1701-1720).—" Medical " discovery of variolation by James Pylarino, and propagation of the method in Greece by Pylarino and Timoni.

Second period (1720-1728).—Introduction of variolation in the West, thanks to the publications of Pylarino and Timoni and to the propaganda of Lady Mary Wortley Montagu.

In addition to the events of this period already mentioned we may draw attention to the following :—

1722. Dr. Le Duc, also a Greek physician, published in Holland a monograph on variolation. The leading British physicians study the method, the first being probably Sir Samuel Garth and Sir Hans Sloane.

1723. Boyleston in Massachusetts begins his inoculations.

1728. By this date there had been 897 inoculations in England with 17 deaths.

Third period (1728-1798).—*Great development and introduction into other countries.*

1748. Introduction of variolation into Holland by Tronchin. Kirkpatrick inoculated in Charleston, South Carolina, between 800 and 1,000 with only 8 deaths.

1750. Inoculation of the children of the Duke of Orleans in Paris by Tronchin. Introduction of inoculation in France.

1754. The Royal College of Physicians declares inoculation to be " highly salutary."

1760. Robert and Daniel Sutton practise inoculation extensively.

1768. Dimsdale inoculates Catherine the Great and members of the Russian Imperial court.

1769. Angelo Gatti performs numerous inoculations in Italy.

1798. Jenner. End of variolation. Beginning of vaccination.

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[*February* 22, 1934, *continued*]

Spontaneous Circumrenal Hæmatoma

By KENNETH HERITAGE, M.S.

ABSTRACT.—By spontaneous circum-renal hæmatoma is meant a condition of extensive extravasation of blood into the kidney bed and surrounding tissues, unassociated with trauma.

Since this is manifested by a fairly uniform clinical picture, by similar operative findings, and by peculiar difficulties in treatment, I propose to discuss it as a clinical entity irrespective of its wide ultimate causation. Very few cases are reported in the English literature. Nevertheless, from the world literature I have collected 170 case reports, and on them, together with three further cases, I base the present paper.

Etiologically the cases fall into three groups :—

(1) Those due to definite disease of the kidney or its blood-vessels, 58%.

(2) Those due to extra-renal causes, 22%.

(3) Those cases whose cause is obscure, 20%.

In the first group neoplasms and inflammations of the kidney, aneurysms of the renal artery and arteriosclerosis are obvious causes. Many cases are due to obstruction of the renal veins.

The classical triad of abdominal pain, signs of internal hæmorrhage, and a tumour in the loin are often obscured by the resemblance of an acute abdominal catastrophe.

In acute cases, expectant treatment is almost invariably fatal. Evacuation of the clot, tamponage and drainage has a mortality of about 40%, whilst nephrectomy in 55 cases showed a mortality of 22%.

RÉSUMÉ.—L'expression hématome para-néphrétique s'applique à une extravasation de sang étendue autour du rein et dans les tissus adjacents, sans traumatisme. Comme cette affection se manifeste par un tableau clinique assez uniforme, par des apparences opératoires semblables, et par des difficultés particulières dans le traitement, je propose la discuter comme une entité clinique, sans prendre compte des nombreuses causes. Le nombre de cas publiés dans ce pays est très petit, mais dans la littérature universelle j'ai pu recueillir 170 cas, sur lesquels, avec 3 cas personnels, j'ai basé le travail suivant.

Du point de vue étiologique ces cas tombent en trois groupes :

(1) Ceux dus à une affection déterminée du rein ou de ses vaisseaux—58% des cas.

(2) Ceux dus à des causes extra-rénales—22% des cas.

(3) Ceux à cause obscure—20% des cas.

Les causes évidentes dans le premier groupe sont les tumeurs du rein, les anévrysmes de l'artère rénale et l'artério-sclérose. Beaucoup de cas sont dus à des obstructions des veines rénales.

Les trois symptômes classiques—douleurs abdominales, signes d'hémorragie interne et tumeur des lombes—sont souvent cachés par la simulation d'une catastrophe abdominale aiguë.

Chez les cas aigus le traitement expectatif est presque toujours fatal. L'évacuation du caillot, avec tamponage et drainage, résulte en une mortalité d'environ 40%, tandis que dans 55 cas la néphrectomie a donné 22% de morts.

ZUSAMMENFASSUNG.—Der Ausdruck spontanes Hämatom des Paranephrium meint eine ausgedehnte Blutung in das Nierenbett und seine benachbarten Gewebe, die nicht mit Trauma verbunden ist.

Weil dieses durch ein ziemlich regelmässiges Krankheitsbild, ähnliche operative Befunde und eigenartige Schwierigkeiten in der Therapie gekennzeichnet ist, werde ich es als klinische Einheit abhandeln, ohne Berücksichtigung auf die breiten Endursachen. Eine sehr kleine Anzahl von Fällen ist in diesem Lande mitgeteilt worden, doch habe ich aus der Weltliteratur 170 Falle zusammengebracht, und habe auf diesen, mit 3 eigenen Fällen, die jetzige Arbeit begründet.

Ätiologisch können diese Fälle in 3 Gruppen verteilt werden:

1. Die durch deutliche Erkrankungen der Nieren oder deren Gefässe verursachte—58%.
2. Die durch extrarenale Ursachen bedingte—22%.
3. Die durch unbekannte Ursachen bedingte—20%.

Die offenbare Ursachen in der ersten Gruppe sind Nierengeschwülste, Aneurysmen der Art. renalis und Arteriosklerose. Viele Fälle sind durch Obstruktion der renalen Venen verursacht.

Die drei klassische Symptome, Leibschmerzen, Zeichen von innerer Blutung, und Lendentumor, sind oft durch Simulation einer akuten abdominellen Katastrophe verdunkelt.

Bei akuten Fälle verläuft die abwartende Behandlung fast immer tödlich. Die Evakuation des Gerinnsel ergibt eine Mortalität von etwa 40%, während aus 55 Fälle die Nephrektomie in 22% tödlich endete.

BY spontaneous circumrenal hæmatoma is meant a condition of extensive extra-renal extravasation of blood into the kidney-bed and surrounding tissues, unassociated with trauma. Since this is manifested by a fairly uniform clinical picture, by similar operative findings, and by peculiar difficulties in treatment, I propose to discuss it as a clinical entity irrespective of its wide ultimate causation. The condition appears to be one of considerable rarity. I have not found a paper on the subject in the English journals or a description of the condition in the standard English textbooks.

From the world literature I have collected 170 case reports, and on them, together with three further cases, I base the present paper.

So far as I am aware, the first reference to the condition is made by Ballonius in his *Opera Omnia Medica*. This book which remained a standard work for the next 150 years, was probably written shortly before his death in 1616. In it he describes the case of a boy aged 12, who was taken ill with a rash. When the rash appeared to be subsiding he began to have hæmatemesis and hæmaturia. He at length died from loss of blood. On opening the body the viscera were seen to be studded with petechiæ and a large quantity of blood was extravasated around the kidneys. In the author's own words "a new symptom-complex was thus discovered."

Since that date a number of contributions have been made to the subject, notably by Pierre Rayer in 1839, and Wünderlich in 1856. Of recent years a large number of individual cases have been reported but, as yet, few—if any—of the difficulties that surround the subject have been solved. Owing to its rarity, a correct pre-operative diagnosis is seldom made, and even at operation the cause of the hæmorrhage often remains undiscovered. Lenk's classical triad of abdominal pain, progressive pallor, and the presence of a tumour in the loin is not always obvious. As my cases show, the symptoms can resemble very closely those of an acute intra-abdominal catastrophe, such as a perforated ulcer. As a rule, the duration of acute symptoms before seeking advice is rather longer than in the cases of perforation. In the later stages progressive enlargement of the hæmatoma, paralytic ileus, uræmia, or intercurrent conditions, are the causes of death. In two cases the acute onset occurred during sleep.

My first case is that of a man aged 51, who having had vague discomfort in the right hypochondrium for several months was seized with violent pain in the right side of the abdomen in February 1928. He vomited and passed blood in his urine. On admission to the London Hospital three days later, the abdomen showed rigidity and deep tenderness especially on the right side. Cystoscopy showed the hæmorrhage to be coming from the right ureter. At laparotomy a large hæmorrhagic mass in the right kidney region was disclosed. Nothing was done and the patient made a good recovery, keeping fairly well until August 1930 when, whilst kneeling on his bed, he

was again seized by severe abdominal pain crossing the abdomen "like a band of fire." He vomited some dark, coffee-coloured fluid once, and blood on two occasions. The pain was very sudden and severe. It commenced in the epigastrium, thence spread all over the abdomen and went through to the back. On admission he was collapsed. Temperature 97, pulse 124.

The board-like rigidity and deep tenderness led two surgeons again to the diagnosis of perforated peptic ulcer. At laparotomy the peritoneum contained blood-stained fluid coming from a large hæmatoma in the region of the right kidney over which the peritoneum was torn. The right kidney region was packed with gauze from in front and the patient again made a good recovery.

One year later he returned with dyspnœa, œdema of the feet, ascites and multiple large abdominal masses—undoubtedly secondary carcinoma. Bilateral retrograde pyelograms showed no gross pelvic deformity. The right pelvis was displaced downwards, but there was no evidence of a primary neoplasm of the kidneys. The urine still showed a trace of albumin and a few red cells. The blood-urea was 36 mgm., and the urinary function was within normal limits. He developed a large left pleural effusion and died at home several months later. Unfortunately no post-mortem examination was obtained.

Case II is that of a retired policeman, aged 65, who, whilst in bed at 6 a.m. twenty hours before admission, was seized with very severe right-sided abdominal pain and had vomited twice. Although the pain had improved after acute onset, it returned with greater severity during the day, and he was sent to hospital as a perforated ulcer.

On admission he was greatly shocked and had marked pallor. Temperature 97; pulse 96. He admitted having suffered recently from indigestion, occurring an hour and a half after food. There were urinary symptoms or hæmaturia. The abdomen showed board-like rigidity. At laparotomy, then made under the diagnosis of perforated ulcer, a little blood-stained fluid was found in the peritoneal cavity. Everywhere, however, the viscera were discoloured by gross retroperitoneal extravasation of blood. This had extended through the mesenteries and between the layers of the transverse mesocolon. The origin of this extravasation was seen to be a massive hæmatoma occupying the right loin, over which the intact peritoneum was stretched, resembling both in size and appearance "a second liver." In view of the collapsed condition of the patient the peritoneum was closed, and a transfusion given; it was hoped thereby to revive him sufficiently to allow exploration of the loin. His condition, however, never allowed of this. He developed a marked degree of paralytic ileus and five days later his blood-urea had risen to 217 mgm. The urine throughout showed a trace of albumin but no other findings. The blood-count showed a severe secondary anæmia and leucocytosis of 24,000. On cystoscopy both ureters were seen to be active in excreting urine, but intravenous indigo-carmine failed to appear in 17 mins. Urine collected by a left ureteric catheter contained 2·04% urea. In spite of intravenous and subcutaneous saline, uræmic delirium rapidly supervened and continued until he died, on the twenty-second day of his illness.

Post-mortem Report (Dr. W. W. Woods).—Bronchopneumonia. Purulent inflammation of submaxillary salivary gland. Hæmorrhage into carcinoma of right suprarenal. Operation: laparotomy.

Hæmatoma, 12 by 12 by 8 cm. (fig. 1, p. 40) containing purple blood-clot and a little fluid blood and lined with adherent blood-clot, in retroperitoneal tissue, above right kidney, and extending in front of its compressed flattened upper pole. Poorly defined compressed portion of right suprarenal in the anterior wall of the hæmatoma. Poorly defined ragged mass (7 by 6 by 4·5 cm.) of opaque, reddish-yellow, friable growth projecting into the hæmatoma near the portion of suprarenal. Friable polyp of growth (1 by 0·8 by 0·3 cm.) projecting into inferior vena cava from the orifice of a right suprarenal vein. Slight diffuse

green hæmorrhagic pigmentation of retroperitoneal tissue throughout abdomen. Normal left suprarenal. Parenchymatous degeneration of kidneys. Adiposity of pericardium. Slight fatty infiltration of myocardium of right ventricle. Clean healing laparotomy wound (19 cm. long) on right side of umbilicus. Moderate atheroma of aorta and its branches.

FIG. 1.—Post-mortem specimen showing site of hæmatoma.

Adenoma (4·5 by 4 by 2·8 cm.) projecting downwards from left lobe of thyroid. A few colloidal cysts (1 cm. diameter) in thyroid. A little glandular tissue in one area in adipose thymus. Leiomyoma (1·5 by 0·8 cm.) projecting from muscularis into submucosa of

fundus of stomach. Two melanomata (0·5 cm. diameter and 0·4 cm. diameter) in skin of right hypochondrium. Very wasted man.

Microscopic examination.—The following tissues were embedded in paraffin: two portions of the growth from the hæmatoma; anterior wall of hæmatoma, including the portion of the right suprarenal; both kidneys; submaxillary gland; stomach with myoma; melanoma of abdominal skin; thyroid with adenoma; thymus. Frozen sections of the left kidney were stained for fat.

Growth from hæmatoma.—There are a few broad anastomosing bands of fibrous tissue containing elastic fibres. Between these the remainder of the tissue is a hæmorrhagic almost entirely necrosed neoplasm, in which masses of blood-clot alternate with areas where "ghosts" of necrosed large polygonal cells lie closely packed in lobules separated by strands of fibrous tissue. In the borders of the necrosed tissue are numerous large spheroidal and polygonal cells whose cytoplasm is frequently swollen, pale and foamy. Here are also numerous round and spindle cells containing brown pigment, as well as lymphocytes and plasma cells. Sparsely scattered throughout the sections are groups of atypical polygonal giant-cells, with very abundant slightly spongy cytoplasm, and a single large irregularly shaped hyperchromatic nucleus, groups of small cells with oval nuclei, and dense net of chromatin and groups of polygonal cells resembling those of normal suprarenal cortex, the latter being sometimes arranged in short broken columns.

Anterior wall of hæmatoma with right suprarenal.—Here there is an almost complete section of partly necrosed suprarenal lying on the surface of the hæmatoma; in the latter only blood-clot can be distinguished.

Kidneys.—The capillaries, interlobular veins and vasa recta of the left kidney are distended with blood; this congestion is slight in the right kidney, outside the capsule of which part of the hæmatoma is seen. There is albuminous degeneration of the cells of the first convoluted and ascending Henle tubules. Many of the straight, collecting and discharging tubules contain hyaline albuminous casts. There is ischæmic degeneration of a few glomeruli.

The points of importance in this case are:—

(1) The acute onset.

(2) The severe paralytic ileus associated with a rising blood-urea and death from uræmia. Although progressively diminishing quantities of urine were excreted, there was never complete suppression, such as occurred in the case of unknown causation reported by Chauvenet.

(3) The difficulty, even at post-mortem examination, of discovering its ultimate cause. It was only with difficulty that the ghost-cells in the clot were found and the neoplastic origin disclosed. It is possible that some of the unexplained cases in the literature have a similar origin, for Case I shows that it is possible for such a patient to survive several years after surgical intervention without showing signs of metastasis.

Case III.—Male, aged 41, seen in June 1933.

He gave a history of chronic alcoholism for years with occasional delirium tremens. In November 1928 he began to have abdominal pain, with anorexia and loss of weight. The pain was located over the eighth costal cartilage one hour after food. About this time he was investigated in Ruthin Castle. Examination of the cardiovascular system showed no abnormality. The blood-count was normal except for a leucocytosis of 10,000. Urine was clear on microscopy.

Radiographic examination of the alimentary tract suggested a quiescent duodenal ulcer. He was given medical treatment. Nine days before I saw him he was taken ill with a return of pain and pyrexia. His doctor found tenderness over the gall-bladder. The pain returned more severely with persistent vomiting. A lump was now palpable in the right side of the abdomen; this increased in size.

On examination: A thin, ill man; temperature 98°. Tongue furred, dry, and indented, resembling the "parrot" tongue of uræmia. The abdomen moved

poorly and a large tender swelling was felt under the right upper rectus; this was thought to be an acutely inflamed gall-bladder. At laparotomy the stomach was seen to be dilated, the duodenum was œdematous and bound down to a large retro-peritoneal mass. An incision was made into this mass on the outer side of the duodenum. A large well-walled-off cavity containing thin brown fluid, old and recent blood-clot, was opened.

The kidney, apparently normal, lay on the outer side; after mopping out of the contents, a tube was inserted into the cavity.

Unfortunately, the patient died about twelve hours later and a post-mortem examination was not obtained.

The 170 cases of spontaneous non-traumatic extra-renal hæmatoma which comprise the literature may be divided into three groups:—

(1) Due to definite diseases of the kidney or its blood-vessels ...	100	58%
(2) Due to extra-renal causes	34	22%
(3) Cause obscure	33	20%

Sex incidence			Renal disease			Extrarenal causes
Males	95	...	Nephritis	30%	...	Suprarenal tumour
Females	61	...	Tumours	22%	...	Perinephric inflammation
Unrecorded	14	...	Aneurysm	20%	...	Blood diseases
			Thrombosis	4%	...	Non-renal aneurysms
	170					

FIG. 2.—Corrosion specimen, showing stellate veins.
(*By kind permission of Mr. Duncan Morison*).

Cases in which even a remote history of trauma is recorded have been excluded. In the first group renal neoplasms, inflammations, nephritis, and aneurysm of the renal artery are obvious causes. The rôle played by venous obstruction is more difficult to access. In several cases of circumrenal hæmatoma complete thrombosis of the renal vein has been found. In a recent article Polkey and Vynaleck showed that experimental ligature of the renal vein in dogs produced parenchymal hæmorrhages in all cases, typical circumrenal hæmatomata in 48·8%, and subcapsular hæmorrhages in 33·3%.

Possibly in this respect the connexion shown to exist between the superficial stellate veins of the kidney and the perinephric vessels via the perforating vessels may be significant. Here is a celluloid corrosion specimen by Mr. Duncan Morison showing the superficial capsular veins (figs. 2 and 3). It is easy to conceive that

FIG. 3.—Celluloid corrosion specimen of human kidney, showing stellate veins and extra-capsular radicle. (*Mr. Duncan Morison.*)

by obstruction to the venous return these veins could be subjected to a degree of engorgement which would end in their rupture. In Groups 1 and 2 venous engorgement due to pressure on the renal vein by tumour or blood-clot may, by setting up a vicious circle, account for the progressive enlargement of the hæmatoma.

GROUP 3.—CASES OF OBSCURE CAUSATION.

Author	Sex	Age	Local condition	Treatment	Result
Barthels	F.	51	Suprarenal destroyed No neoplasm	Decapsulation of kidney	Death
Bonthius	F.	55	No cause	Nephrectomy	Cured
Breitner	F.	22	No cause	Drainage	Died
Brunner	F.	55	No cause	Drainage	Died
Chauvenet	F.	59	No cause	Drainage	Death
Cordier	M.	60	Bilateral circumrenal	None	Died
Droubaix	F.	62	Suprarenal	None	Died
Fedoroff	F.	32	Pararenal cyst	Drainage	Cured
Fedinec	F.	33	No cause	Drainage	Died
Fowler	F.	52	No cause	Nephrectomy	Cured
Gutierrez	F.	34	No cause	Drainage	Cured
Heilman			No cause	Nephrectomy	Cured
Hullsiek	F.	49	Pararenal cyst	Nephrectomy	Cured
Lejars	F.	49	Suprarenal	Exploration	Died
Leopold	F.	33	No cause	Nephrectomy	Cured
Pauchet	F.	53	No cause	Drainage	Cured
Picque	F.	35	No cause	Nephrectomy	Cured
Rayer	M.	75	Suprarenal	None	Died
Rayer	M.	65	Suprarenal	Drainage	Cured
Reuss	M.	6/365	Suprarenal	None	Died
Ritter	M.	29	No cause	Drainage	Died
Schultze	F.	29	No cause	Drainage	Cured
Tage-Hansen	F.	35	No cause	Drainage	Cured
Walther	F.	22	No cause	Drainage	Cured
Hildrebrand	F.	19	No cause	Drainage	Cured
Koch	M.	29	No cause	Drainage	Death
Mackenzie	M.	35	Polycythæmia	Nephrectomy	Cured
Padtberg	M.	54	No cause	Drainage	Died
Saint-Cene	M.	34	No cause	Nephrectomy	Cured
Polkey-Vynalek	F.	39	No cause	Drainage	Cured
Greco	M.	54		Drainage	Cured

In Group 3, although the cause is unknown, the kidney seems to be the most likely source of the bleeding. This is supported by the frequent finding of blood and albumin in the urine, and by the fact that recovery and prolonged survival follow nephrectomy. In none of the cases, however, was an actual bleeding point seen at operation, and on microscopic section the removed kidneys showed no change except venous congestion, and in some cases tiny parenchymal hæmorrhages. In eight cases of unexplained origin where drainage plus nephrectomy was performed all the patients survived, whilst of nineteen in which drainage alone was carried out only ten patients survived.

In some cases the extrarenal hæmorrhage ceases spontaneously, the hæmatoma becomes encapsulated and forms a pararenal blood-cyst. Several such specimens are to be found in the museums.

Treatment.—Several writers, notably Israels, Doll, and Polkey and Vynalek, state that in all cases of circumrenal hæmatoma treated expectantly the patients die. Although this is so in all reported cases, it may be explained by the fact that the diagnosis is as a rule established with certainty only at operation or post-mortem examination. It is possible that in some cases the growth resolves or becomes encysted as previously mentioned. It must be accepted, however, that cases with acute symptoms have a high mortality when untreated. Whilst no rule of treatment can be laid down, it is interesting to note the results recorded from surgical intervention.

RESULTS

All cases	Cases	Deaths
Expectant treatment only	50	50
Drainage only	51	23
Nephrectomy plus drainage ...	54	14
Cases of obscure causation		
Expectant treatment only	4	4
Drainage only	19	9
Nephrectomy plus drainage ...	8	0

Where a grossly diseased kidney is the source of the bleeding, nephrectomy will be carried out. The same applies to cases of aneurysm of the renal artery or thrombosis of the renal vein. In cases of extrarenal origin the prognosis is poor, unless a blood vessel can be caught and ligated in situ—to judge from the literature a very rare occurrence. Where the kidney seems normal, no cause can be found and no bleeding vessel seen, the best results appear to follow nephrectomy. When this is unjustifiable, evacuation of the clot, packing and drainage are advisable.

I would like to thank the members of the staff of the London Hospital for permission to record their cases, and particularly Mr. V. W. Dix, who first operated on Case I.

JOINT DISCUSSION No. 5

Section of Ophthalmology and Section of Dermatology

Chairman—A. C. HUDSON, F.R.C.S. (President of the Section of Ophthalmology)

[*February* 9, 1934]

DISCUSSION ON THE CONDITIONS COMMON TO OPHTHALMIC AND DERMATOLOGICAL PRACTICE, SUCH AS ROSACEA, STYES, ECZEMA, ETC.

Mr. J. H. Doggart: These two branches of medicine overlap each other in many different ways, and they have enough common ground to provide discussion for a series of combined meetings, although I doubt whether we could reasonably expect the dermatologists to attend a series which would be far more profitable to us than to them. This I say because I believe that many of the cases which come to ophthalmic clinics are really skin cases, and could be transferred to a skin department with at least equal chances of obtaining correct diagnosis and successful treatment. I refer especially to some of the varieties of blepharitis, about which I intend to speak later.

The overlapping of our respective subjects falls naturally under three headings. First, there are numerous diseases in general medicine which commonly implicate the skin and the eyes. For example, measles will cause conjunctivitis, and possibly corneal ulcers, as well as a rash; thyroid deficiency has been known to produce multiple opacities in the corneal substance associated with the characteristic skin changes of myxœdema, and these manifestations have simultaneously disappeared after a course of glandular extract. In the second place, the eyeballs need the protection of the eyelids, which are covered by facial skin. Now certain neoplastic and inflammatory conditions of the skin, as exemplified by rodent ulcer and lupus, show a predilection for the face. Moreover, some cases of blepharitis are merely incidental to the clinical condition of facial seborrhœa, against which treatment must be directed before we can expect any lasting improvement in the lid condition. Thirdly, there are a few skin diseases in which the investing membranes of the eyeball itself may undergo damage. Rosacea is the most important malady in this group, which also includes pemphigus and dermatitis herpetiformis.

Perhaps the first of these categories offers the widest field for discussion concerning diagnosis, but for that reason I intend to avoid it, and will confine my remarks mainly to one example from each of the other two groups, namely, blepharitis and rosacea. I hope some other speaker will enlighten us concerning styes and their treatment. They often appear to result from conjunctivitis, or from some

other local eye condition. In many other cases they are associated with pustules elsewhere, an expression of lowered general resistance to staphylococci. On the other hand, we frequently see people develop styes during a spell of good health, in the absence of any conspicuous local infection, and without any staphylococcal outbreaks in other parts of the body. There may be successive crops lasting for months. Such protracted visitations arouse the anger of the victims—or of the victims' parents, the victims often being children. The lay mind observes with bewilderment that our profession, having furnished a cure for many a disease that used to be fatal, is yet unable to abolish the stye and the common cold. A number of different substances have been tried hypodermically, intramuscularly, or by the mouth, for repeated styes of doubtful origin. Among these remedies, perhaps, the autogenous vaccine has the best reputation among ophthalmic surgeons in this country. It would be interesting to hear whether anyone has been able to assess the value of vaccines by experience gained from a large number of cases.

Blepharitis.—For teaching purposes, blepharitis is often divided arbitrarily into a mild, or squamous, and a severe—or ulcerative type. Clinical practice, however, provides cases that show all grades of severity, and I doubt whether the conception of a definite dividing-line has any value. In the great majority of cases, blepharitis at its onset is probably due to some variety either of conjunctivitis or of facial dermatitis. When appropriate measures are directed against its radical cause, blepharitis rapidly diminishes, unless the causative variety of conjunctivitis or dermatitis happens to be severe and chronic. Long-continued blepharitis is, however, often seen in the absence of any conjunctivitis, and unassociated with any obvious disorder involving the skin of the rest of the face. Such cases, which are relatively far more common in hospital than in private practice, are frequently attributable to neglect or improper treatment in the early stages, leading to persistence of the blepharitis long after its original cause has subsided. As a result of hot, gritty, irritable sensations at the lid margins, many patients get into the habit of rubbing the affected skin, and thus spread and prolong any infection that may be present. Another injurious practice on the part of many people is the repeated plucking-away of inspissated secretion from the roots of the lashes without any preliminary softening by means of lotion. Others suffer from the employment of dirty pieces of wool, gauze, or rags in the toilet of the lids. The longer it endures, the more will blepharitis approach the ulcerative form, which is characterized by scantiness and irregular growth of the eyelashes.

Concerning the treatment of this condition, it is obvious that any associated conjunctivitis or facial dermatitis must be dealt with, but there is probably wide divergence of opinion on the question of what preparations may most advantageously be applied to the lids. In many of these cases the condition is aggravated by over-treatment, and it matters little what lotion is used, so long as powerful solutions are avoided. Normal saline, or some other mild remedy, should be used sparingly. Accumulated crusts of dried secretion ought to be gently sponged away by means of clean wool applied in the direction of the lashes, after thorough moistening by means of lotion. In most cases lotion should not be used more than three times a day. Petroleum jelly or weak boracic ointment may be applied to the lid margins before sleep, and possibly once more during the day time. In certain cases, especially in those which have undergone a long course of treatment, the skin of the lids becomes sodden and fissured by excessive moisture. This difficulty is less likely to arise if care is taken to dry the skin by gentle dabbing with clean wool after each bathing. It may, however, occur in spite of all precautions, and is best combated by discontinuance of the lotion until the excoriated skin has had a chance to heal.

The response to any particular remedy varies widely even among those patients whose blepharitis presents the same essential features. The same patient may react in an inconstant way to the same treatment used at different times. Therefore

it is advisable to try a different preparation whenever progress is long delayed, but some cases drag on indefinitely, whatever treatment is adopted, and in spite of all precautions against uncleanliness and fresh sources of irritation. In my opinion the ætiological importance of refractive errors has often been exaggerated. It is, however, advisable to ascertain the refraction in all persistent cases, and to correct any errors that may be present. However small may be its direct influence, eye-strain can exert a considerable indirect effect by prompting the patient to rub his eyes.

Rosacea.—Rosacea remains inseparable from alcoholism in the mind of the lay public, but most medical men realize that abstinence is no guarantee against rhinophyma. Dr. J. D. Rolleston's [1] interesting historical notes on this disease show that the reputation of alcohol as a constant ætiological factor was being questioned in the early part of the eighteenth century. Later in the same century, according to Dr. Rolleston, a certain physician divided rosacea into nine varieties, one of which was alleged to arise from excessive water drinking, and to be curable by the administration of wine.

In discussing the ætiology of rosacea, many writers convey the impression that ill-health is nearly always associated, and it cannot be denied that a large number of these patients suffer from indigestion and other troubles. Not uncommonly they are over-anxious about the minor misfortunes of life. On the other hand, many of them seem to be healthy and happy. Concerning the relative frequency of ocular complications, I was surprised to hear Dr. Dore say, a few years ago, that he did not remember having seen more than six examples. It would be interesting to hear whether most other dermatologists testify to the same rarity. Ophthalmic out-patients convey a false impression of the frequency of these complications. In addition to the self-evident reason that they would not be there unless their eyes were being troublesome, it must be remembered that rosacea keratitis is an obstinate disease, tending to relapse, so that many patients get into the habit of attending more than one clinic.

In nearly every case of rosacea, a mild blepharitis develops sooner or later, not associated with distortion of the lid margins, but undoubtedly predisposing to the formation of meibomian cysts, so commonly seen in this condition. Rosacea conjunctivitis is accompanied by watering of the eyes and intolerance to light. Some cases display, on the ocular conjunctiva near the corneal margin, small greyish-yellow nodules resembling those that occur in phlyctenular disease. Except in the mildest cases, the conjunctivitis of rosacea signifies impending keratitis, whose earliest manifestation usually consists of vascular loops invading the edge of the cornea. Rosacea keratitis is a serious handicap to ordinary activities. A bad case may relapse many times a year, and so incapacitate the patient from doing regular work. With each successive attack, the new-formed vessels tend to progress towards the centre of the cornea. Ulcers, infiltrates, and interstitial pustules frequently supervene. These ulcers may be attended by tissue destruction rapid enough to produce localized thinning of the cornea, which may subsequently become distorted into a state of irregular astigmatism, or even may undergo perforation. The drawings [shown] illustrate vascularized opacities in a case of recurrent rosacea keratitis. Note the typical wedge- and tongue-shaped opacities, and the characteristic sparing of the upper as compared with the lower half of the cornea.

A few years ago I had under periodical observation a large number of rosacea patients, whose reaction to treatment was, on the whole, disappointing. I will quote from a paper [2] written at that time, mentioning several of the fallacies which may exaggerate the value of any form of treatment.

"It is necessary to emphasize that the course of the disease is frequently irregular. Long spontaneous remissions may occur. Thus, in one middle-aged woman, who had

suffered from repeated severe corneal attacks at intervals of a few months, all manifestations ceased for a period of nearly two years, during which time she was having no treatment of any kind. Although a respite of such duration is rare, yet the possibility of it must be borne in mind, lest extravagant hopes be raised by the apparent success of a therapeutic measure in one isolated case. Good results have been claimed for different methods of treatments on inadequate evidence. No case, however neglected, remains in the acute stage for many months. Should a long remission happen to follow any attack treated in a special way, then that form of treatment is apt to receive the credit for what may well have been a coincidence. No method should be commended until it has benefited a considerable number of cases. Moreover, there is a distinct tendency on the part of acne rosacea to give a temporarily favourable response to a new method of attack. A change of treatment may work like a charm the first time it is tried. Later, when the patient has come to believe that at last a real cure has been found, another attack will obstinately resist the treatment which had promised so well. It would be safe to assume that many apparent cures in the literature were merely examples of momentary improvement."

Although severe keratitis may be associated with scanty signs on the face, or, on the other hand, there may be little or no keratitis, in spite of a pronounced facial efflorescence, yet, in any particular case, it is usual to find close correspondence between the corneal and facial outbreaks in the sense that fresh infiltrates in the eye seldom occur in the absence of renewed skin activity. Therefore it would be unreasonable to expect a permanent cure for rosacea keratitis unless the skin lesions could unquestionably be prevented from recurring. So far as I know, a method of complete cure is still lacking, as one might have supposed from the number and variety of the remedies advocated. It is true that the frequency and severity of the attacks will often decline with the approach of old age, but meanwhile the corneæ may have become entirely opaque.

REFERENCES

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2 Doggart, J. H., "The ocular complications of acne rosacea," *Brit. Journ. of Ophthal.*, 1931, xv, 446-457.

Dr. H. Semon: The problem of rosacea is one which lends itself well to a combined discussion of this kind. It has been variously ascribed to abnormalities of the nasal mucosa, to derangements of the gastro-intestinal tract, particularly of the relative acidity of the gastric juice, on which a considerable amount of work has been done in this country, by Ryle and Barber, W. H. Brown and others, and finally to disturbances of the uterus and adnexa at or about the menopause, at which time the symptom is most frequently observed.

The only way, it seems to me, in which it would be possible to reconcile the interaction of factors in areas so remote from each other, is to assume the presence of nervous disturbances at the periphery of a sort of reflex arc in the sympathetic nervous system, with which both the nasal, gastric, and uterine mucosa and adnexa are known to have particularly intimate connexions.

The rapid appearance and reappearance of flushing in certain areas, viz., naso-labial folds, alæ nasi, cheeks, chin and forehead, so characteristic of rosacea, suggest the intervention or association of angioneurotic factors—a point which is further supported by the similarly located mechanism of ordinary blushing, in which the sympathetic system undoubtedly plays an important part. Whatever the genesis of these abnormal stimuli, their constant recurrence and protraction ultimately lead to chronic stasis and congestion which, viewed by the capillariscope (Rost) is seen to be most pronounced in the small vessels of the upper horizontal network in the cutis, associated with a spasmodic constriction of the capillaries in the papillary body.

Such a congestive state leads sooner or later to disturbances of secretion and infection of the sebaceous glands, and at this point the frank symptoms of rosacea, with its erythema, papules, and pustules, become apparent, and the ultimate tendency to hypertrophy (the end-result of which may be rhynophyma), and telangiectases, as may occur with any chronic intermittent form of vascular stasis and low-grade inflammation, can be explained. The theory of a nervous mechanism is further supported by the aggravation of the symptoms produced by emotion, heat and cold, light and other physical stimuli, while, on the other hand, it is interesting to note that carefully graduated doses of X-rays have a beneficial effect, partly, no doubt, because they tend to inhibit the excessive sebaceous activity so frequently present, and possibly because, as is held in some quarters, radiotherapy has a sedative action on the so-called vegetative nervous system.

If the patient is a seborrhœic subject, with an oily skin and a scurfy head, and occasional attacks of acne or furunculosis, the tendency to aggravation by rosacea will receive a further impetus, and thus may be explained the occurrence of blepharitis with or without conjunctivitis. That explanation seems to me, however, to fail in the case of the corneal complications, for if vascular congestion and paresis are accepted as the prodromal stages in the genesis of rosacea of the skin, how can these be of ætiological importance in an avascular tissue, such as the cornea?

The answer to that question is not facilitated by Triebenstein's pronouncement that keratitis is commoner than blepharitis, chalazion and the other marginal infections, attributable to rosacea, and I shall be interested to hear if the statistics of other ophthalmologists are in accord with that finding.

Cranston Low, writing in the *British Journal of Dermatology*, 1922, xxxiv, 275, on the association of eye lesions with rosacea, finds little difficulty in bracketing conjunctivitis with the areas of dilated capillaries found on the skin, corneal phlyctenular lesions with the papular eruption, and keratitis with the pustular stages of the complaint. It is an attractive theory, but perhaps a little too simple. An arena such as this offers ideal opportunities for its discussion.

The large majority of rosacea cases are soon relieved, if not permanently cured, by attention to certain dietetic rules and the administration of alkalies, or acids. I think we must admit that dermatologists are still somewhat divided on this issue. There are those who prefer the older alkaline treatment and those who have been persuaded in recent years, by a preponderance of hypochlorhydric findings, to give hydrochloric acid. The cases seem to do equally well on both, but sometimes show aggravation if the acid is given too strong, or to a patient with obvious gastritis. My own practice is still to give carbonate of magnesia and bismuth, with or without a little bromide and valerian in emotional cases, for a week or two before embarking on the more aggressive treatment by hydrochloric acid. The patient must rigidly abstain from alcohol and from strong tea and coffee, and it may be said, without fear of contradiction, that tea is a more common factor in the production of rosacea than alcohol, which has been much maligned in this connexion in the past. Condiments such as pickles, chutney, mustard and vinegar should be taken sparingly or not at all, and drinks are best taken cold or tepid, and between rather than with the meals. Foci of sepsis about the teeth, chronic tonsillitis and constipation must also receive appropriate treatment, and exposure to extremes of temperature should be avoided. Local applications usually with ichthyol and lead (1%) in calamine lotion should be given in acute or irritable cases, and sulphur and resorcin in the same strengths in the more chronic varieties. Very resistant cases and those in which a seborrhœic element is pronounced are usually benefited by carefully graded doses of X-rays.

Dermatitis of the eyelids.—I confess to considerable difficulty in defining the limitations and in classifying the types, the ætiology, and the treatment of the cases to be discussed under this heading. A mild inflammation may cause nothing more

characteristic than simple œdema, and in this situation may be confused with the effects of renal or cardiac disease. It is presumed that such are excluded by the terms of reference. As dermatologists we should, I think, classify such cases as are referred to us as primary or secondary in origin. In the former we are always confronted by the problem of causation, without the solution of which our treatment must be empirical, and recurrences frequent and unpreventable. Most, if not all, such cases are the result of an irritant—the "antigen," reacting in a delicate epidermal structure of a predisposed or "allergic" individual. Allergy may be inherited or congenital, or acquired, and it is an accepted axiom that every epidermis may become allergic or sensitized provided that the antigen is applied in the right concentration and in sufficiently repeated dosage. Thus the late Bruno Bloch found that he could sensitize and eczematize the skins of 100% of his guinea-pigs to an etherial extract of the primula plant, provided the applications were continued long enough. It would seem to follow that the susceptibility of a subject to an irritant is not a specific reaction in the narrow sense, but one shared by all epidermal tissues *in varying degree.*

Of all epidermal structures that of the eyelids would appear to be the most delicate, and when, therefore, the irritant is conveyed from without—exogenous —as it mostly is, the eyelids are very frequently the first to show signs of irritation. Dermatitis due to a hair-dye may first become manifest in this situation, while a similar susceptibility to plants, powders, scents and the vapour of formic or osmic acid, may first be heralded by swelling and irritation in this situation. The number of such irritants seem to grow from year to year with the advances in synthetic chemistry, both civil and military, and there must be many of my present audience who still retain a lively recollection of the appalling, if only temporary, disability in this connexion caused by mustard gas in the later stages of the War.

In comparison with the exogenous antigens, the circulating or endogenous causes would appear to be very few. Even the bacterial cases contract their infection for the most part from without, and the majority of such are really secondary to some such condition as seborrhœa, which, I think it will be agreed, is one of the commonest causes not only of dermatitis of the lids, but of styes, and blepharitis as well. Once it has been acquired, the allergy of the individual may be extreme. The minutest traces of the offending substance may suffice to aggravate or rekindle the dormant susceptibility. Quite recently I was consulted by a lady, aged 30, on account of swelling and irritation of the eyelids. She had just returned from the country where she had been helping to repaint some cottage furniture. In default of other demonstrable causes I suspected the possibility of sensitization to turpentine or some other constituent of the paint, ordered a simple boracic lotion for bathing the eyes, and was informed a week later that the inflammation had completely subsided. I was much surprised to hear that on the tenth day the trouble had recurred, although not so severely as before. On causing an inquiry to be made it was discovered that painters were at work in the basement of the London house in which she was living, and although no trace of the smell of paint could be detected in the rooms above, it seems reasonable to suppose that there was sufficient to provoke a relapse, for soon after she arrived in Switzerland, where she still is, all vestige of the dermatitis had disappeared.

In such cases the so-called "patch" test, which should always be made when there is any doubt of the true cause or nature of the dermatitis, has much to commend it, and should never be omitted in any case in which subsequent legal procedures may be expected.

The treatment of cases of primary dermatitis is very simple, provided that the cause has been ascertained. Remove or prevent access of the cause, and the case recovers spontaneously. The obvious corollary is unfortunately not infrequent, and in these sometimes we should welcome the help and collaboration of our

ophthalmological colleagues. There may be hidden causes in errors of refraction, in mydriatic applications, and even in the substitutes for tortoiseshell used for making spectacle frames. We, on the other hand, may be of some assistance in the seborrhœic cases, for there is no doubt that infections of the scalp—pityriasis capitis—and of the face, often go hand in hand with a marginal blepharitis, and may continue to reinfect the marginal follicles, eventually causing loss of the lashes and the complications resulting therefrom. I have often thought that the degree of eyelash destruction present in a case of chronic seborrhœic dermatitis is an index of the severity of the infection, and a guide to the ultimate prognosis. I further believe that the difficulties of treatment in these chronic cases and the prevention of relapses in dermatological clinics are even greater on the ophthalmological side, and we shall gain much by the mutual statement and elaboration of our methods of attack.

It has to be realized that in seborrhœa and its manifold complications we are dealing with a tendency or diathesis, and that treatment, in order to be effective, must above all be persistent. It will be admitted that very few cases in which the chronic disease is once established are permanently cured. Seborrhœa is really in the same category as a host of other chronic tendencies, and until we are aware of all the causes at work we must content ourselves with measures designed to alleviate and prevent relapses, for we can no more control the actual cause than we can that of gout, diabetes, or constipation.

Of all local remedies, sulphur is still the best, but it must not be prescribed in too concentrated a form, and must be watched carefully lest irritation supervene—a very common occurrence in the treatment of scabies. Resorcin and salicylic acid are good substitutes, and colloidal and other less irritant forms of sulphur may take its place at times. Sulphur spas offer many facilities to patients with the time and money to spare. The selection of a vehicle or base for the active ingredient depends upon the stage or acuity of the infection, and the particular area to which it is to be applied. An oily or greasy base is generally indicated for the dry scurfy scalp, and frequent tar shampoos should be ordered to clear away detritus of scales and grease. On the body a lotion in the acute stages, or in the flexures where moisture predominates a paste of starch, vaseline, and lanoline in various combinations, as the dermatitis subsides, and the parts become dry.

The permutations and combinations of all the various remedies and their various indications are signs, alas, of the slender control which therapy can exercise, and the seborrhœic is certainly among the group of patients who wander from one clinic to another, and from spa to spa, according to the season of the year.

But if the outlook as regards cure is bad, that which follows neglect is infinitely worse, and no small a portion of our daily routine is devoted to the encouragement and treatment of the sorely tried seborrhœic.

Mr. R. Affleck Greeves: The ocular lesions of acne rosacea bear a striking resemblance to those of phlyctenular disease. Corneal lesions are the commonest; they usually occur as single or multiple localized infiltrates in the superficial layers of the cornea and may appear in any part of the corneal area. The overlying epithelium breaks down and an ulcer forms; these ulcers are extremely resistant to treatment and often become vascularized, forming fascicular ulcers. When they heal, they leave an appreciable amount of scarring, seriously affecting the sight if central in position, and almost invariably keep on recurring so that a wide area of cornea ultimately becomes involved. I have not found that the recurrences are necessarily associated with exacerbations of the skin lesions.

Another less common variety of lesion begins as an infiltrate at the corneo-scleral junction and spreads into the cornea from there, giving rise to a marginal

ulcer. Inflammatory infiltrates may also occur in the episcleral tissues. These do not ulcerate but look and behave like ordinary episcleral foci of a localized type: they are not so resistant to treatment as the corneal lesions. In a few cases I have seen actual phlyctenules at the limbus, exactly resembling those usually seen in children; these lesions are conjunctival and so more superficial than the corneo-scleral lesions already described.

The most characteristic clinical feature of the disease is its obstinacy and the repeated appearance of fresh lesions whether the old ones are healed or not.

As regards treatment, acne rosacea is of course a manifestation of some constitutional disturbance and the logical method of tackling these cases would be to cure this, which, unfortunately, is more easily said than done. It is believed that a disturbance of the digestive system is the primary cause and a matter of common knowledge that in some cases dilute acids taken internally have a marked beneficial effect.

With regard to local treatment, I have found that the eye lesions, like those of phlyctenular disease, respond best to stimulation and for this reason I put the patients on perchloride of mercury lotion and yellow oxide of mercury ointment, with, of course, atropine, which relieves the pain and photophobia. It is a mistake, I am sure, to cover the eye with a pad; again, as with phlyctenular cases, the eyes do not take kindly to being bandaged, whereas dark glasses give great relief.

I do not approve of carbolizing the ulcers; this may tend, if anything, to make them worse. The greatest relief, however, in my experience, is given by X-ray applications, a method of treatment which I first advocated in a paper read before the Ophthalmological Society of the United Kingdom in 1930.[1] A single early application of X-rays may cause a recent infiltrate to disappear and a short course of repeated applications often effects healing of old chronic ulcers. These applications also have a most beneficial effect in relieving the pain which is so distressing a feature of the disease, and I may add that I have never seen any harmful results; as one would expect, there is no visible reaction to such a small dose.

Although fresh attacks are almost bound to occur, the intervals between the recurrences are usually greatly lengthened by this treatment; as I have already said, owing to the persistence of the constitutional cause it is obvious that a complete cure cannot be obtained by means of any purely local measures. As in all forms of treatment for disease of any kind, some patients undoubtedly respond much more readily than others.

The technique of the X-ray applications is described in the paper to which I have referred.

Dr. Sibyl Eastwood said that during the last seven or eight years Dr. A. M. H. Gray had afforded her, at University College Hospital, the opportunity of studying and attacking the problem of rosacea from the point of view not of the ophthalmologist or the dermatologist but of the general physician. In the cases sent to her she was interested in trying to elucidate the digestive symptoms. In a series of several hundred cases some digestive disturbance had been present in 95%. Digestive complaints often had to be elicited by a good deal of cross-questioning, especially as the degree of the digestive trouble was sometimes comparatively mild. The underlying factor in rosacea was a vascular congestion of the face, originating as a reflex from other parts of the body, in most cases from the stomach. Since Dr. Barber and Dr. Ryle published their findings in regard to the gastric secretion in subjects of the disease, people had talked as if hydrochloric acid was always deficient. But Brown's paper in 1925, and her (the speaker's) own work later, had shown that this was not so. Only about 48% of cases of rosacea had either achlorhydria or a

1 *Trans. Ophth. Soc. U.K.*, 1930, l, 111.

deficient secretion of hydrochloric acid; in 40% the secretion of it was normal; in only 10% was it high. Correlation of the clinical and X-ray findings with the pathological investigation of gastric secretion suggested that reflex flushing always meant a motor disturbance of the stomach. Abnormalities in hydrochloric acid secretion were only important in so far as they disturbed motor function, and the results of treating rosacea were equally good whether dealing with low or high acid curves, so long as smooth and regular peristalsis and emptying could be achieved.

The most promising cases of rosacea were those in which the patient had a low hydrochloric acid secretion, for if they were given hydrochloric acid they recovered. Patients of this kind had gone on well for five or six years, so long as they continued to take the acid, and if there were recurrences they were only mild ones. Equally successful cases were those which had pyloric spasm with a very high acid content, and were treated with alkalies. Some of the failures with these cases were due to the idea that they could be adequately treated by giving alkalies or acid without trying to find out, in each case, which was needed. The need having been ascertained, the administration was ordered accordingly, and the treatment could of course be given with more confidence. A number of hypochlorhydric patients improved if acid was given with their meals, followed by alkali one and a half or two hours afterwards, so as to reproduce the normal cycle of digestion. It was valuable to go into the dietetic factor in each case, and the successes were, largely, in the patients who could carry out the requirements in this respect. Diet was at least as important in treatment as the correction of secretory defects. She agreed that alcohol was not a great factor in the causation of rosacea; tea and excess of starchy foods were much greater sinners.

One speaker had suggested that rosacea was much commoner in women than in men. She (Dr. Eastwood) thought that in making that statement the speaker had overlooked the æsthetic factor; men did not come to hospital or to their medical men for mild degrees of it so much as women did. In most of the cases in which ocular complications had occurred the patients were somewhat devitalized and many had already had recurrent attacks, and had stayed in the house chiefly for many years. For these it was good to give general ultra-violet light baths, all parts of the body except the face being exposed to the rays.

She considered that if this problem were treated not as a dermatological nor as an ophthalmological one, but as a general medical problem, and every effort made, first by correct diagnosis and then by appropriate treatment, to restore the patient's general health to normal, the recurrences would be diminished in number, and the condition would gradually fade out altogether.

Dr. S. H. Browning said it was difficult for him to say anything useful about any of the conditions discussed, because he felt that if he, as a bacteriologist, were to say anything about results from vaccine therapy, a good many people would come forward and say that the patients would have recovered without it.

He was interested in the subject of seborrhœa, because several persons were sent to him for a bacteriological examination of their eyelids, whereas what they needed was not a bacteriologist, but a dermatologist, as they were suffering from seborrhœa of the scalp, or pityriasis capitis. The seborrhœic condition disappeared if one began with the scalp and worked downwards if necessary. The blepharitis which he saw, was due mostly to *Staphylococcus aureus*. He did not think that the *S. albus*, which was sometimes seen, was of much account in affections of the eye. Naturally, suitable cases were treated with vaccines—very useful adjuncts in the treatment of other eye conditions.

Styes were often unassociated with other staphylococcus manifestations in the body. They were very acute in some cases. There was no treatment at present

available for acute staphylococcal conditions. If treatment with vaccines was decided upon in chronic cases it took some time before the vaccine had any effect. But progress was being made in the bacteriological world, and shortly there would be produced a staphylococcal toxoid suitable for acute cases. At present it was the chronic recurring conditions which yielded best to vaccine treatment. Some cases did not get well on this treatment, and that might be because those who dealt with them were on the wrong track. At one time all the cases were thought to be due to the *Staphylococcus aureus*. By taking ordinary smears, or by culture, that organism was obtained, but if a medium containing potassium tellurite was used, cases have been reported to contain streptococci, which had been missed by the ordinary culture methods.

From Culpepper he had learned that if a patient had boils and certain skin diseases acid should be given in plenty. Hydrochloric acid given four or five times a day, in water, was excellent for cases of styes and boils. Cases of carbuncle would improve on the same treatment.

The Chairman said he wondered if Dr. Browning had seen his (the speaker's) two cases of choroiditis. One patient had had acne vulgaris pustules with a metastatic choroiditis, and had been treated with a staphylococcus vaccine. The other patient was a boy with active choroiditis, in whose case there was recently obtained *Staphylococcus albus* from a pustule on the cheek, and also from a pustule on the neck. It was always important to remember the possibility that these eyelid conditions were due to skin infections.

With regard to styes, he wished to raise the question of the danger of early operation. If the patient had an indurated stye and could not sleep because of the pain, what was the risk of incision being followed by serious consequences, such as cavernous sinus thrombosis? Had any member had experience of such a catastrophe?

Mr. Eugene Wolff said that Dr. Semon had stated that in acne rosacea the eyes and the skin were probably affected together, because they had the same sympathetic supply. Mr. Doggart had shown on the screen pictures in which the lower part of the cornea (i.e. the portion not covered by the upper lid) was affected. As far as he (the speaker) knew there was no difference between the sympathetic supply of the corneal vascular plexus above and below; and he had wondered how far exposure played a part in producing the acne rosacea lesions in the eye.

Mr. J. Foster said that apparently on the Continent it was not uncommon for blepharitis to be treated very much as dermatologists in this country treated seborrhœic dermatitis in other parts of the body, namely, by exposure to X-rays. Apparently there existed in this country a prejudice against that treatment for eye conditions, on the ground of possible damage to the eye. Had members had any experiences on this point?

Dr. A. C. Roxburgh said he had had a number of cases of blepharitis sent to him at St. Bartholomew's Hospital by Mr. Cole Marshall which he had been able to improve by small doses of X-rays; some, indeed, seemed to have been cured by that treatment. Though one could not confidently speak of "cure," it was a better treatment than some others. He had never seen any damage to the eye result, as the dose was so small.

Mr. B. W. Rycroft: Ocular pemphigus, although common to the specialties of dermatology and ophthalmology, occurs with extreme rarity in either. Various statistics testify to this fact; Steffan reports 1 in 84,000 eye cases and Pusey notes 2 cases of pemphigus per 1,000 skin cases. I have only been able to trace three cases during the last five years at the Royal London Ophthalmic Hospital.

Before 1858, the disease was confused with various conjunctival degenerations such as hyaline, colloid, and xerotic, but in that year White Cooper first described the entity as "essential shrinking of the conjunctiva." The identification with pemphigus vulgaris came from von Graefe in 1879. The pathology has always been obscure. Sections from the conjunctiva show lymphoid infiltration of the sub-epithelial layers, but no specific change has been described. So also with the bacteriology of the condition: A large diplococcus has been isolated from the bullæ but in animals it failed to reproduce the disease. Some say that syphilis is a cause: others, that it is related to foot-and-mouth disease since it frequently occurs in butchers (see Case 4, p. 96).

Clinically, there are two types, acute and chronic. Acute pemphigus occurs as part of a generalized bullous eruption. Frequently the termination is fatal, but in patients who survive, cicatrization is not a prominent feature. Chronic pemphigus occurs in three types: (1) with vesicles on the skin also; (2) with vesicles on mucosa such as mouth, rectum, etc.; (3) with no evidence of vesiculation elsewhere.

Chronic ocular pemphigus attacks older people in equal proportions and about half of the cases show vesicles. After the rupture of the vesicles cicatrization occurs, binding lids and globe by a firm union of cicatrized conjunctiva. Finally the nutrition of the cornea fails, and xerosis follows with opacity leading to permanent blindness. The differential diagnosis of a skin lesion and conjunctival vesiculation lies between: (1) Dermatitis herpetiformis, in which the vesicles occur in crops. (2) Erythema multiforme, which rarely attacks the mucosa. (3) Bullous syphilides.

The treatment makes a doleful story and remedies have included all the fashionable collyria, followed by mucous grafts, pyretotherapy and auto-hæmotherapy with no avail.

Latterly, I have, by courtesy of the Radium Institute, been able to follow the effects of radiation. There has been a definite improvement in the case treated, but I feel that this is due to the reduction of vascularity rather than to a true cure of this disease.

CASES.

(1) **Unusual Coloration of Sclerotics.**—P. G. DOYNE, F.R.C.S.

This case appears to be almost an exact replica of that shown before this Section by Mr. Foster Moore in February 1930.[1]

The patient, Miss N. (an actress), has noticed that her eyes have been gradually getting blue. She first became aware of this by other people's comments, about five years ago. The bulbar conjunctiva appears of a bluish colour. The palpebral conjunctiva is affected only slightly, if at all. The coloration extends on to the caruncle where it appears brown.

On examination with a slit-lamp, a fine punctate deposit is seen on the bulbar conjunctiva. On the caruncle the deposits are larger in size. Examination of the cornea shows some thickening of the reflex of the posterior cornea surface.

To the patient's knowledge she has not applied silver nitrate to the eye. The only thing that she has used is a blue grease-paint pencil when making-up, in order to darken the lids on the outer surface.

[1] *Proceedings*, 1930, xxiii, 841 (Sect Ophthal., 53).

She has been on the stage over twenty years, but the discoloration has appeared within the last five years. Dr. Browning reports that the pigment present in the grease-stick is manganese sulphide.

(2) **Neurofibromatosis of the Choroid, Ciliary Body and Limbus. Intra-ocular extension of a plexiform neuroma of the fifth cranial nerve.** —JOHN FOSTER, F.R.C.S., and CYRIL POLSON, M.D.

The photograph shown (fig. 1) is that of a woman with neurofibromatosis of the left ophthalmic division of the fifth nerve. A small area of this has been removed for section. Three months ago the eye on this side became blind and

FIG. 1.

painful, and was excised under retrobulbar anæsthesia. The short ciliary nerves were visible at the time of operation, owing to their neurofibromatous development.

Naked-eye examination of a hemi-section of the globe showed a small swelling of whitish colour at the limbus and a notable lack of pigment at the equator of the choroid, which in this region was white. Thickening of the choroid was not apparent to the eye, but micrometer measurement of the histological specimens showed that it had a maximum thickness of 1·0 mm. near the posterior pole. Elsewhere the average thickness, except at the equator where the choroid was only 0·05 mm. thick, was about 0·5 mm.

Microscopical appearances of the choroid.—Diffuse neurofibromatosis in the posterior and anterior thirds, but not apparent in the equatorial region. In the

latter the choroid was apparently atrophic and deficient in pigment. The neurofibromatous tissue disturbed—and tended to obscure—the normal layers of the choroid; this tissue consisted, for the most part, of large spindle-shaped cells with large oval nuclei. A number of oval bodies, about 50 micra by 20 micra, consisting of oval nuclei packed within a delicate capsule and resembling "nerve-endings," were present, especially in the posterior third. There appeared to be

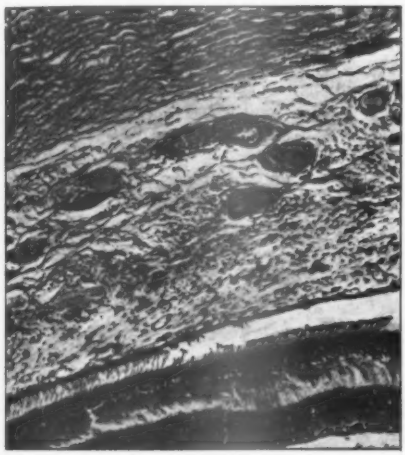

FIG. 2.—Showing sclera, choroid and medium enlargement of retina.

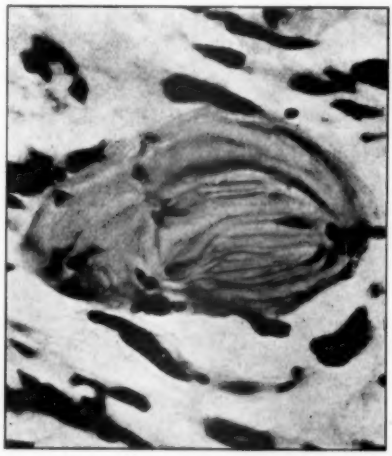

FIG. 3.—Nerve-ending, to show coiled structure.

excess of pigment in the neurofibromatous areas, and here also the blood-vessels were less conspicuous than in healthy choroid. The appearances were almost identical with those described by Parsons. (Figs. 2 and 3.)

Neurofibromatous tissue was also present in the ciliary body, and the swelling at the limbus was composed of similar tissue; there was slight extension on to the outer aspect of the sclera. The ciliary nerves at the posterior pole, extra-ocular, presented the appearances seen in plexiform neuroma.

(3) **Pemphigus Conjunctivæ.**—B. W. RYCROFT, F.R.C.S. (by courtesy of Mr. A. SORSBY).

J. T., male, aged 70, painter and decorator.

History.—Nine years ago a "patch" appeared on the left eye. Eighteen months ago the right eye became irritable and the left eye one month later. Epilation was repeatedly carried out. There has been intermittent throat trouble, and "blisters" in the mouth were found after the onset of the eye condition. There has also been nasal discharge. No history of vesicles of the skin.

Past ophthalmic history.—No previous eye trouble.

Examination.—Symblepharon right and left eye; aberrant lashes; no xerosis; corneæ relatively uninvolved. There are many ulcerated areas on the fauces, gums, and lips, also central ulcer of the hard palate. Wassermann reaction negative.

Treatment.—Vaccines. This case has not been treated by radium.

(4) **Pemphigus Conjunctivæ.**– B. W. RYCROFT, F.R.C.S.

J. D., male, aged 55, butcher.

History.—The left eye became irritable two years ago, and the right eye six months later. History of "blisters" in the mouth at the time. No recent illness; no previous skin trouble; no accident or injury to the eyes; no eye trouble in the family.

Past ophthalmic history.—No previous eye trouble. No history of conjunctival blisters.

Examination.—Right eye: Upper and lower symblepharon; aberrant lashes. Left eye: Symblepharon; pannus; aberrant lashes; no xerosis.

Cultures.—*B. xerosis; Staphylococcus aureus;* Wassermann reaction negative.

Treatment.—Surface application of radium; six hours' duration; 10 mgm. radium, 1 mm. silver screen. There have been three applications and the condition has improved.